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BLOOD AMINO NITROGEN LEVELS

Changes in Blood Amino Nitrogen Levels Following Ingestion of Proteins and of a Protein Hydrolysate in Infants with Normal and with Deficient Pancreatic Function

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THIS paper is a preliminary report of the results of studies of blood amino nitrogen levels after the ingestion of test feedings of protein and of acid hydrolysates of protein. The study was undertaken to learn whether there were any characteristics of the peripheral blood amino nitrogen curve after the ingestion of these test feedings that would make it possible to distinguish between the various nutritional diseases of infants. Particular attention has been given to this amino nitrogen response in infants with congenital cystic fibrosis of the pancreas. It was hoped that the procedure would give information of diagnostic value, as well as help in the evaluation of certain therapeutic measures in common use. The first part of this paper deals with the use of the procedure as a diagnostic method and the second with its use as a guide in the evaluation of therapy.

There have been a number of attempts to put to use the quantitative determination of the amino nitrogen content of the blood in the study of disease. Historically, Van Slyke and Meyer,[1] in 1912, demonstrated the presence of amino acids in the blood of animals and an increase in the level of amino acids after the ingestion of protein. This was soon verified by other workers, using similar and other technics. Folin and Berglund[2] in 1922 first demonstrated this postprandial rise in man. Efforts to use the rate and degree of this rise as a test of hepatic

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1. Van Slyke, D. D., and Meyer, G. M.: The Amino Acid Nitrogen of the Blood: Preliminary Experiments on Protein Assimilation, J. Biol. Chem. **12**:399-410, 1912.

2. Folin, O., and Berglund, H.: The Retention and Distribution of Amino Acids with Especial Reference to Urea Formation, J. Biol. Chem. **51**:395-418 (April) 1922.

function have been attempted but, in the main, have been unsuccessful. Witts,[3] using this method, found no significant difference in health and in hepatic disease. Weicher[4] and, later, Kirk[5] were unable to show abnormalities of retention of plasma amino acids following their ingestion by patients with hepatic disease. Lockwood and Davies,[6] using test meals of gelatin and aminoacetic acid, were unable to show any variation in the amino acid curve for various abnormal mental states. Barber and Oriel[7] made similar absorption studies on patients with allergic manifestations but drew no final conclusions. In general, all of the work so far reported has shown only that the degree of amino-acidemia increases after the ingestion of certain proteins and amino acids and that the amount of the increase seems to be little affected by disease. Likewise, the fasting blood amino nitrogen level has been found to be of little diagnostic significance.

No attempt has been made, however, to demonstrate by this method the faulty digestion of protein caused by absence of pancreatic enzymes in the duodenal juice. That such a defect exists in infants and children with cystic fibrosis of the pancreas has been well demonstrated by Shohl, May and Shwachman[8] with balance studies and by Andersen[9] with stool analyses, both demonstrations showing diminished retention of dietary protein. It has been clearly established that the lack of trypsin in the duodenal juice of these children so diminishes digestive proteolysis that the absorption of digestive end products of the protein in a diet normally considered adequate is insufficient to cover their needs. Such failure of absorption should be reflected in the amino nitrogen levels of the blood after ingestion of native protein. It was also considered that peculiarities in the absorption of amino acids might occur in patients with celiac disease but with normal duodenal enzymes and in patients with other nutritional disorders. These studies were therefore done on a varied group of patients, including 7 with cystic

3. Witts, L. J.: Observations on the Metabolism of Amino Acids in Health and Disease, Quart. J. Med. **22**:477-491 (April) 1929.

4. Weicher, B.: Ueber den Nachweis gestörter Teilfunktionen als Grundlage funktioneller Leberdiagnostik, Ztschr. f. d. ges. exper. Med. **81**:481-505 (April) 1932.

5. Kirk, E.: Amino Acid and Ammonia Metabolism in Liver Diseases, Acta med. Scandinav., 1936, supp. 77, pp. 1-147.

6. Lockwood, M. R., and Davies, D. R.: Blood Urea Changes in Abnormal Mental States After the Administration of Amino Acids, Biochem. J. **26**:745-752, 1932.

7. Barber, H. W., and Oriel, G. H.: A Clinical and Biochemical Study of Allergy, Lancet **2**:1009 (Nov. 17) 1928.

8. Shohl, A. T.; May, C. D., and Shwachman, H.: Studies of Nitrogen and Fat Metabolism on Infants and Children with Pancreatic Fibrosis, J. Pediat. **23**:267-279 (Sept.) 1943.

9. Andersen, D. H.: Celiac Syndrome: II. Fecal Excretion in Congenital Pancreatic Deficiency at Various Ages and with Various Diets, with Discussion of the Optimal Diet, Am. J. Dis. Child. **69**:221-230 (April) 1945.

fibrosis of the pancreas, 21 with malnutrition due to other causes and 4 normal infants.

Enzymatic or acid hydrolysates of protein would seem to be of value in the treatment of infants with cystic fibrosis of the pancreas. Shohl and his co-workers [8] found that a positive nitrogen balance could be more easily maintained and that nitrogen in the stools was considerably diminished when an enzymatic hydrolysate of casein was fed. Substitution therapy with pancreatin has also been demonstrated to be of value in the treatment of cystic fibrosis of the pancreas. An attempt has been made in these studies to show the increased absorption of an acid hydrolysate of casein as compared with intact casein by determining blood amino nitrogen levels after the ingestion of each food. In other studies pancreatin was given simultaneously with casein to infants with pancreatic deficiency and determination of blood amino nitrogen levels were made after the feeding. By such absorption curves, it was hoped that a new method of evaluating therapy might be developed.

METHOD OF STUDY

In general, the method here used for studying absorption of amino acids resembles the dextrose tolerance test. The patient fasts for eight to ten hours, this period being kept at a minimum for small infants. After a fasting specimen of blood is obtained, the protein or protein hydrolysate is administered by mouth, and for five hours thereafter specimens of blood are taken at varying intervals. This report deals with the amino nitrogen curves obtained following the ingestion of casein, gelatin, an acid hydrolysate of casein, and a combination of casein and pancreatin.

A. Preparation of the Test Feedings.—The source of casein was a commercial preparation (Casec [10]) composed chiefly of calcium caseinate. This is more soluble than pure casein, thus better adapted to infant feeding, and is of constant composition. The test feeding, except when noted to the contrary, consisted of a mixture of 1.7 Gm. of Casec (containing 1.5 Gm. of protein) and 1 ounce (30 cc.) of water per kilogram of actual body weight. For the larger infants and children, water was added in an amount roughly one and one-half times the volume of the dry Casec. As the infants could not be depended on to take any of the test meals by nipple, the test feedings were usually given by gavage.

The pancreatin preparation used in conjunction with Casec in some of the test meals was given as enteric-coated granules,[11] dispensed in capsules

10. Mead, Johnson and Company, Evansville, Ind. Composition of Casec: protein (nitrogen × 6.38), 88 per cent; milk fat, 2.0 per cent; minerals, 4.5 per cent, and moisture, 5.5 per cent.

11. Parke, Davis & Company, Detroit.

containing 0.32 Gm. Two capsules were used with the test meal, the contents of one being spilled in the child's mouth before and the second following the feeding by gavage. When the granules are mixed with the feeding, they tend to plug the gavage tube.

The test feeding of gelatin was made in the same way as that of casein, with 1.74 Gm. of gelatin [12] (containing 1.5 Gm. of protein) and 1 ounce (30 cc.) of water per kilogram of actual body weight. To liquefy and homogenize the mixture, it was heated to body temperature or slightly above just before administration.

The protein hydrolysate used was an acid hydrolysate of casein [13] containing 0.021 Gm. of nitrogen per cubic centimeter. Except when the contrary is noted, the amount used was equivalent in nitrogen content to the test feeding of Casec. Casec was considered to contain 0.125 Gm. of nitrogen per gram. For 2 of the older patients with cystic fibrosis of the pancreas, this amount of the protein hydrolysate was incorporated in a flavored gelatin preparation (Jello) containing "Jello" powder, corn syrup and a small amount of lemon juice. This preparation is palatable and was taken willingly by mouth, which obviated feeding by gavage. In the cases in which masking with the gelatin preparation was not done, the hydrolysate was diluted with water to make a total volume of 1 ounce per kilogram of body weight and was given by gavage.

All of these test meals were found to produce a definite rise in the blood amino nitrogen level in normal infants, and their consistency and volume were tolerated well. The feedings were prepared the night before the test and kept in the refrigerator overnight. To be sure the infant received all of the feeding, ½ to 1 ounce (15 to 30 cc.) of the required water was reserved from the mixture for final rinsing of the bottle.

B. Collection of Blood Specimens.—The number of blood specimens taken after the ingestion of the protein or of the hydrolysate depended on how smooth and complete a curve was desired. In those infants considered to exhibit normal absorption, the maximum elevation of amino nitrogen with all test meals occurred, with few exceptions, between one-half and two and one-half hours after the protein was ingested, and the original fasting level was approached within five hours. For our purpose it was found that little information would be sacrificed if only 5 specimens were obtained: fasting, one-half hour, one and one-fourth hour, two and one-half and five hour specimens. In many cases early in the study specimens were taken more frequently.

Either capillary or venous blood may be used. However, the rise in amino nitrogen following ingestion of protein is greater in

12. Charles B. Knox Gelatine Co., Inc., Johnstown, N. Y.
13. Parenamine, Frederick Stearns & Company, Detroit.

arterial than in venous blood. This is explained by the exit of amino acids from the tissues into the blood during the fasting state, which makes the venous fasting level greater than the arterial. Conversely, after a protein meal amino acids leave the capillaries to enter the tissues, and this results in a venous level lower than the arterial level. In cats, Bolton and Wright,[14] using Folin's original colorimetric method of determining blood amino nitrogen, found this arterial-venous difference to be 0.2 to 0.4 mg. per hundred cubic centimeters, both during the fasting state and after the protein feeding. The total difference in amino nitrogen response to protein would thus be 0.4 to 0.8 mg. per hundred cubic centimeters greater if arterial blood were used. On these grounds, capillary blood, coming from small arterioles, would seem to reflect more striking changes in the amino nitrogen level than would venous blood. This source was used in most of these studies.

The capillary blood was collected directly from a heel or finger tip puncture in a pipet calibrated to deliver 0.2 cc.; the column was brought to the mark, and the blood was then blown into a centrifuge tube containing 6.0 cc. of tungstic acid precipitating solution. The pipet was rinsed by blowing this solution through it several times, and the precipitating agent and the blood were thoroughly mixed by inverting the tube. The difficulties and sources of error encountered in this method are common to its use for other chemical determinations. Bubbles may be sucked into the pipet, or the blood may clot before it can be blown out. These difficulties may be overcome if both heels are immobilized and if a free flow of blood is obtained before collection is started. It is of greatest importance that no pressure be exerted on the heel to facilitate the flow of blood, inasmuch as tissue juices, which may enter in this manner, are notably much higher in amino acid content than is blood. Despite precautions, these errors did occur, as manifested by occasional blood amino acid values which obviously ranged widely from the expected value. Because of this, 2 to 4 specimens were taken in most cases at each time interval, and the results were averaged or discarded according to a criterion of accuracy statistically developed from the results of multiple determinations on single specimens of venous blood. Such procedure divorces errors arising from the collection of capillary blood from errors inherent in the actual chemical determination of the amino nitrogen.

Criterion of Accuracy: This criterion of accuracy was arrived at by calculating the sigma values for five sets of 16 determinations of blood amino nitrogen made on each of 5 specimens of oxalated venous blood. The average of these five sigmas was found to be $\pm$ 0.20. The standard errors of the means averaged $\pm$ 0.05. All five sets had highly significant t values. It was considered reasonable to

14. Bolton, C., and Wright, G. P.: The Absorption of Amino Acids and Their Distribution in the Body Fluids, J. Physiol. **89**:269-286 (April 9) 1937.

expect the multiple determinations with capillary blood to check within two sigma distances (in the case of duplicates and triplicates) or within the standard error of the mean (with quadruplicates). Results of the capillary blood determinations for each time interval were thus averaged or discarded according to the following standards. If duplicates did not check within 0.40 mg. per hundred cubic centimeters (two sigma distances), both determinations were discarded and no value was recorded for that time interval. If one value of a triplicate determination did not check within 0.40 mg. per hundred cubic centimeters of either one of the other two values, it was discarded, and the value recorded was the average of the other two. If the average of all four values of quadruplicates was 0.05 mg. per hundred cubic centimeters (standard error of the mean) away from the average of the three most in agreement, then the latter average was recorded as the value for this time interval. If the averages of the four values checked within 0.05 mg. per hundred cubic centimeters of the average of the three most in agreement, the average of all four values was the recorded value.

Application: On the basis of this criterion, 88 of 920 determinations made to furnish the data given here were discarded. Thus 9.56 per cent were considered to be in error. Of these, 75 per cent were discarded because the value was too high. This led us to believe that contamination of the specimen with tissue juice was the greatest source of error, although precautions were taken not to squeeze the heel. No relation could be discovered between the per cent of determinations discarded and the type of test meal used. Likewise there was no relation between the per cent discarded and the level of blood amino nitrogen at the time the specimens were taken. As all the specimens were collected by one person, errors resulting from individual variations in the technic of obtaining the specimens were kept at a minimum. However, as the study progressed chronologically, a higher proportion of the determinations were discarded. Of the 460 specimens taken early in the study, 4.8 per cent were discarded, while 14.8 per cent of the 460 determinations made in the last half of the study were discarded. This is in part due to the fact that more quadruplicate specimens at one time interval were taken in the last half of the study, from which, because of the more stringent criterion used, more determinations were discarded.

No complications attributable to the numerous heel pricks involved in running a test developed in any of the patients.

C. Method of Blood Analysis.—In determining the level of blood amino nitrogen, the micromethod of Krauel,[15] which requires only 0.2 cc. of blood, was used. As described before, the blood was pipetted directly from a puncture of a heel or finger tip and was delivered into a tube containing 6.0 cc. of tungstic acid precipitating solution. No attempt will be made here to describe the technic of the determination.

15. Krauel, K. K.: The Microdetermination of Amino Acid Nitrogen in Blood with the Spectrophotometer and with the Optical Colorimeter, J. Lab. & Clin. Med. **29**:222-227 (Feb.) 1944.

Some modifications were necessary to adapt the procedure for use with the Evelyn photoelectric colorimeter. The filtrate solutions were diluted to approximately 10 cc. before heating, and after heating they were immediately cooled in ice water rather than in running water. The final dilution was 25 cc. to give a greater range of values with the Evelyn colorimeter. A 470 micron filter was used. We found that exactness in the time of heating and immediate cooling in ice water were essential in obtaining duplicable results.

Some comment is in order concerning the accuracy of the method of blood analysis used here as a measure of the amino acid content of the blood. By far the most accurate of all methods is the manometric ninhydrin method of Hamilton and Van Slyke.[16] However, the larger amount of blood required, as well as the elaborate apparatus and technic, makes this method unsatisfactory for a clinical study with small infants. Folin's original colorimetric method,[17] introduced in 1922, from which the method used here is derived, has undergone many modifications improving on its accuracy. It is based on the reaction of amino nitrogen with sodium β-naphthoquinone sulfonate to produce a red color. This reaction is not entirely specific for amino nitrogen, however. Its discrepancies have been extensively studied by Frame, Russell and Wilhelmi.[18] Proline and hydroxyproline, both containing nitrogen in the imino form only, produce color with the reagent but in only half the intensity expected from amino nitrogen. Both amino groups of lysine and ornithine react, giving twice the intensity of color produced by most other amino acids. Thus, as has been pointed out by Hoffman,[19] the constantly changing combinations of amino acids in the blood probably give slightly different light absorptions for the same quantity of amino acids and nitrogen. Other nitrogen-containing substances, naturally or unnaturally occurring in the blood, may likewise react with the reagent.[18] This is true of ammonia, uric acid and all of the sulfonamide compounds. Thus the actual amino nitrogen values obtained with this method are, at best, approximations. Yet results are duplicable, and amino acids added to blood may be quantitatively recovered. In a study such as the one presented here, in which comparative changes

16. Hamilton, P. B., and Van Slyke, D. D.: The Gasometric Determination of Free Amino Acids in Blood Filtrates by the Ninhydrin-Carbon Dioxide Method, J. Biol. Chem. **150**:231-250 (Sept.) 1943.

17. Folin, O., and Wu, H.: A System of Blood Analysis: A New Colorimetric Method for the Determination of the Amino Acid Nitrogen in Blood, J. Biol. Chem. **51**:377-391 (April) 1922.

18. Frame, E. G.; Russell, J. A., and Wilhelmi, A. E.: The Colorimetric Estimation of Amino Nitrogen in Blood, J. Biol. Chem. **149**:255-270 (July) 1943.

19. Hoffman, W. S.: A Photometric Adaptation of the Folin Method for Determination of Plasma Amino Acid Nitrogen, Am. J. Clin. Path. **15**:57-60 (July) 1945.

in the blood following ingestion of amino-acid-containing food are measured in a number of persons, the method is practical and satisfactory.

To facilitate the correlation and graphing of data, the blood amino nitrogen values have been reduced to a zero fasting level. Deviations of these values below the fasting level have been designated as negative quantities.

I. CHANGES IN THE AMINO NITROGEN CONTENT OF THE PERIPHERAL BLOOD FOLLOWING INGESTION OF PROTEIN (CASEIN AND GELATIN) IN PATIENTS WITH AND WITHOUT PANCREATIC DEFICIENCY

SELECTION OF PATIENTS

The patients on whom these studies were done were between the ages of 1 week and 2 years with the exception of 1 child with cystic fibrosis of the pancreas, who was 6 years old. In order to present the results obtained after the casein test meal in organized form, the patients on whom these curves were made were placed in five groups. Those in groups 1, 2, 3 and 4 at no time showed evidence of pancreatic deficiency. With several, the diagnosis of cystic fibrosis of the pancreas was suspected at the time of admission but was ruled out by finding a normal trypsin content in the duodenal juice. All those in group 5 had cystic fibrosis of the pancreas.

GROUP 1. *Four Normal Infants.*—All of these infants had good appetites, were normal in weight and gaining and had no sign of infection or disease that would interfere with utilization of protein. Only a few are presented in this group because of the few available for study.

GROUP 2. *Eleven Undernourished Infants Showing No Sign of Infection at the Time Tests Were Run.*—They were all definitely underweight for their age and birth weight. As can be seen by the diagnoses in table 2, a number presented feeding problems which were difficult to characterize, as the cause was frequently obscure.

GROUP 3. *Eight Poorly Nourished Infants with Concomitant Infection or with Diarrhea.*—Diarrhea was present in 4, 2 having a mild degree at the time the tests were run and the other 2 having a history of prolonged diarrhea ending one to two weeks previously. In no case was there any pathogenic organism isolated from the stool prior to or immediately following the tests, or was there any evidence of a parenteral infection. In the other 4 infants in this group, infection was present in the lungs or pleural cavity.

GROUP 4. *Two Infants with Celiac Disease.*—The case of neither was classic. In both the onset was at 6 months, relatively early in life. However, both had had typical-appearing celiac stools (no stool analyses

were done), had suffered from anorexia, were extremely irritable and responded to a regimen for celiac disease. Neither showed extreme wasting, but both were definitely undernourished. Both had a normal content of trypsin in the duodenal juice. Five absorption curves were done on these 2 patients.

GROUP 5. *Seven Patients with Cystic Fibrosis of the Pancreas.*—The criteria for diagnosis were the typical history and clinical picture and the absence of trypsin in at least 2 specimens of duodenal juice obtained on different occasions. In 1 case (J. G.) the diagnosis was confirmed at autopsy. A total of thirteen curves were made for this group.

Patients Given Test Feedings of Gelatin.—Test feedings of gelatin were given to at least 1 patient in each of the five groups previously mentioned (table 6). A total of ten curves were obtained following this test meal.

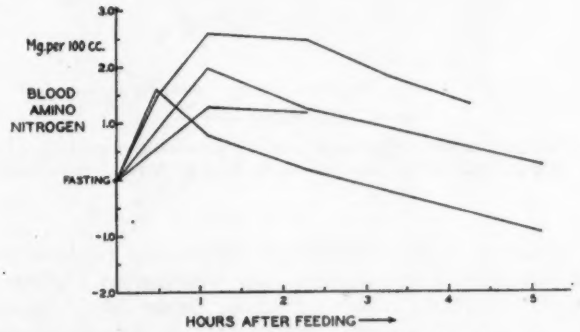

Chart 1.—Amino nitrogen absorption curves following ingestion of casein by normal infants (group 1).

TABLE 1.—*Changes in Blood Amino Nitrogen Following Ingestion of Casein by Normal Infants (Group 1)*

Patient	Age	Weight, Kg.	Protein (Casein) Content of Test Feeding, Gm./Kg.	Blood Amino Nitrogen, Mg. per 100 Cc. Fasting	½ Hr.	1¼ Hr.	2¼ to 2½ Hr.	3¼ Hr.	4¼ Hr.	5 to 5¼ Hr.
M. B.	9 mo.	7.86	1.5	4.35	....	1.29	1.21	....	....	....
W. J.	2 wk.	3.08	1.5	4.57	1.54	2.60	2.47	1.82	1.34	....
H. M.	1 wk.	3.50	1.5	6.05	....	1.97	1.22	....	....	0.24
K. B.	10 wk.	3.75	1.5	5.01	1.59	0.78*	0.19	....	....	0.95

* Venous blood determination.

RESULTS

GROUP 1. *Test Feeding of Casein to Normal Infants (table 1, chart 1).*—The greatest elevation of the blood amino nitrogen occurred at one and one-fourth hours for all patients in this group except 1 (K. B.). This patient's curve reaches a peak at one-half hour with a rapid decline thereafter. The curves for this group resemble each other in that they all rise promptly, exceeding 1.0 mg. per hundred

cubic centimeters within one and one-fourth hours after the test feeding is given, and approach the fasting level in five hours.

GROUP 2. *Malnutrition Without Concomitant Infection* (*table 2, chart 2*).—These curves resemble in a general way those found for

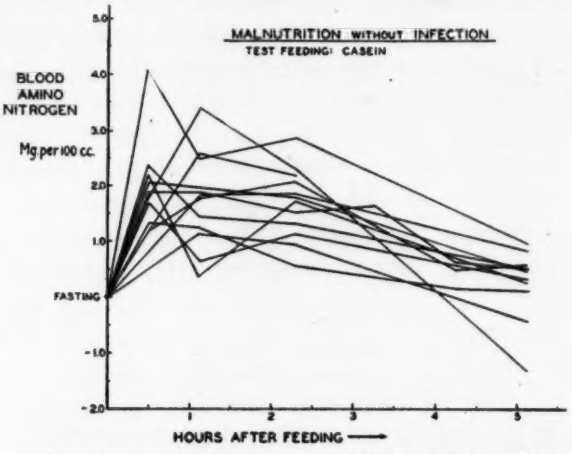

Chart 2.—Amino nitrogen absorption curves following ingestion of casein by malnourished infants having no infection and having normal pancreatic function (group 2).

TABLE 2.—*Changes in Blood Amino Nitrogen Following Ingestion of Casein by Malnourished Infants Having No Infection and Having Normal Pancreatic Function (Group 2)*

Patient and Age	Weight, Kg.	Protein (Casein) Content of Test Feeding, Gm./Kg.	Blood Amino Nitrogen, Mg. per 100 Cc. Fasting	½ Hr.	1¼ Hr.	2¼ to 2½ Hr.	3¼ Hr.	4¼ Hr.	5 to 5¼ Hr.	Comments
W. T. 6 wk.	3.66	1.5	5.38	....	2.57	2.18	....	....	....	Eight days after pylorotomy
M. M. 1 yr.	4.91	1.5	5.75	2.05	....	1.78	....	....	0.48	Anorexia and vomiting
B. G. 6 mo.	3.863	1.5	5.13	1.32	1.23	0.57	....	0.16	0.11	After resection of 42 cm. of ileum
B. G. 7 mo.	3.91	1.5	5.48	0.57	1.12	0.94	....	....	0.41	After resection of 42 cm. of ileum
C. L. 2 yr.	7.80	1.5	6.31	1.77	3.38	1.29	....	....	—1.30	Inactive tuberculosis; patient gaining weight
H. W. 1 yr.	5.45	1.5	5.10	....	1.83	1.84	....	....	0.84	Microcephalic idiot
V. R. 4 mo.	4.66	1.5	5.27	4.08	2.48	2.84	....	....	0.94	Birth injury with convulsions
T. G. 15 mo.	8.86	1.5	6.31	2.36	1.44	1.31	....	....	0.54	Feeding problem
V. P. 6 mo.	4.63	1.5	5.87	2.19	0.36	1.72	....	....	0.28	Feeding problem
C. E. 4 mo.	4.32	1.5	4.29	1.18	1.76	2.04	....	0.49	0.58	Eczema and feeding problem
S. D. 6 mo.	4.20	1.5	4.55	1.87	1.87	1.50	1.62	0.63	0.51	Multiple congenital musculoskeletal anomalies
L. S. 9 wk.	3.58	1.5	7.36	1.70	0.63	1.11	....	....	0.33	Intracranial sp. hemorrhage

normal infants, showing the same range of individual variation. A number of them show considerable irregularity. The two lowest curves obtained for any patient with normal pancreatic function with this test meal are found in this group. Both were for the same patient (B. G.), who deserves special comment. This infant boy had a long congenital reduplication of the ileum necessitating a resection of most of the ileum (43 cm.) and establishment of an ileotransverse colostomy. This had been done several months previously, and in the interim he had failed to gain weight despite an enormous appetite and a good caloric

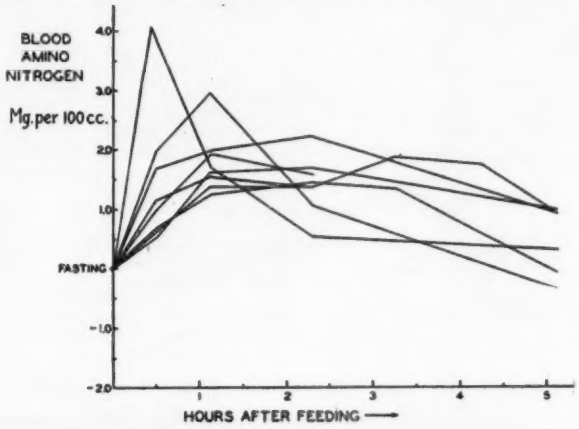

Chart 3.—Amino nitrogen absorption curves following ingestion of casein by malnourished infants having concomitant infection or diarrhea but with normal pancreatic function (group 3).

TABLE 3.—*Changes in Blood Amino Nitrogen Following Ingestion of Casein by Malnourished Infants Having Concomitant Infection or Diarrhea But with Normal Pancreatic Function (Group 3)*

Patient and Age	Weight, Kg.	Protein (Casein) Content of Test Feeding, Gm./Kg.	Blood Amino Nitrogen, Mg. per 100 Cc.							Comments
			Fasting	½ Hr.	1¼ Hr.	2¼ to 2½ Hr.	3¼ Hr.	4¼ Hr.	5 to 5¼ Hr.	
S. A. 3 mo.	3.63	1.5	6.38	1.98	2.94	1.08	....	....	—0.35	Mild chronic diarrhea
G. C. 10 mo.	5.22	1.5	4.19	0.51	1.57	1.69	1.42	....	0.99	Chronic pneumonia
D. L. 8 mo.	5.45	1.5	4.84	0.98	1.95	1.58	....	....	....	Convalescent from prolonged diarrhea
D. S. 3 mo.	2.84	1.5	3.54	....	1.37	1.37	....	....	....	Premature; mild diarrhea
M. C. 5 wk.	2.88	1.5	7.43	4.08	1.70	0.52	....	....	0.30	Mild chronic diarrhea
C. S. 8 mo.	6.70	1.5	4.35	1.12	1.56	1.35	1.88	1.73	0.94	Empyema with open drainage
M. H. 18 mo.	6.25	1.5	5.23	0.68	1.23	1.45	1.34	....	—0.08	Severe chronic pneumonia; cirrhosis of liver
S. L. 13 mo.	5.90	1.5	5.80	1.67	1.98	2.22	....	....	0.92	Convalescent from severe whooping cough and pneumonia

intake. The failure to gain was attributed to diminished intestinal absorptive surface. This we believe to be reflected in the low curves consistently obtained with this infant.

GROUP 3. *Malnutrition with Concomitant Infection or Diarrhea (table 3, chart 3).*—The presence of infection or diarrhea does not seem to affect the configuration of these curves. They resemble closely those in the other groups having no pancreatic disease.

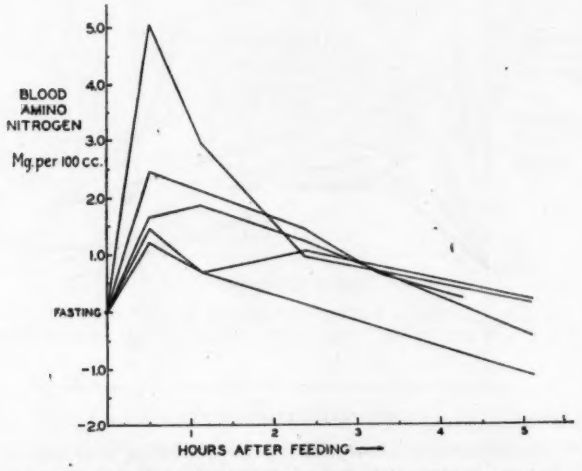

Chart 4.—Amino nitrogen absorption curves following ingestion of casein by infants with celiac disease (group 4).

TABLE 4.—*Changes in Blood Amino Nitrogen Following Ingestion of Casein by Infants with Celiac Disease (Group 4)*

Patient	Age	Weight, Kg.	Protein (Casein) Content of Test Feeding, Gm./Kg.	Blood Amino Nitrogen, Mg. per 100 Cc.						
				Fasting	½ Hr.	1¼ Hr.	2¼ to 2½ Hr.	3¼ Hr.	4¼ Hr.	5 to 5¼ Hr.
E. D.	8 mo.	4.43	1.5	5.06	2.46	2.09	1.44	0.66	0.23	....
E. D.	8 mo.	4.20	1.5	5.18	1.67	1.88	1.25	....	....	—0.45
E. D.	10 mo.	5.22	1.5	5.93	5.06	2.97	0.98	....	....	0.15
M. G.	1 yr.	5.84	1.5	7.69	1.56	0.77	....	....	....	—1.09
M. G.	1 yr.	5.91	1.5	6.45	1.30	0.76	1.08	....	....	0.23

GROUP 4. *Celiac Disease (table 4, chart 4).*—With 1 exception all curves reach a peak at one-half hour in this group. This feature is not limited to these patients only, as nearly half of all the curves for patients with normal pancreatic function showed this one-half hour peak. Whether it is consistently found with this disease will be determined only after a larger series of patients have been investigated. The highest curve in this group was obtained for E. D. when she was 10

months old. In the two months between tests she had shown considerable clinical improvement. Whether the greater elevation correlates with the improvement can only be speculated on until further data are available.

While showing much individual variation, the curves following a test meal of casein for all patients without pancreatic disease, as shown in the first four groups, have a number of common characteristics.

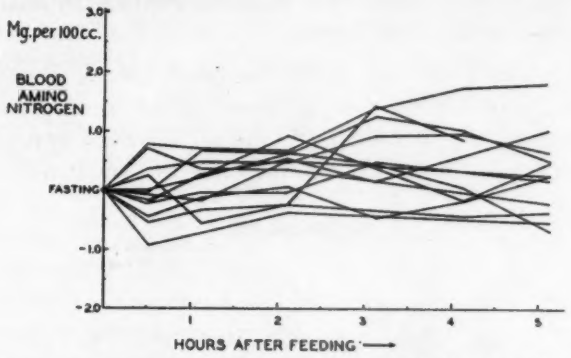

Chart 5.—Amino nitrogen absorption curves following ingestion of casein by infants and children with cystic fibrosis of the pancreas (group 5).

TABLE 5.—*Changes in Blood Amino Nitrogen Following Ingestion of Casein by Infants and Children with Cystic Fibrosis of the Pancreas (Group 5)*

Patient and Age	Weight, Kg.	Protein (Casein) Content of Test Feeding, Gm./Kg.	Blood Amino Nitrogen, Mg. per 100 Cc. Fasting	½ Hr.	1 to 1¼ Hr.	2 to 2¾ Hr.	3 to 3¾ Hr.	4 to 4¼ Hr.	5 to 5¼ Hr.	Comments
S. B. 6 yr.	19.10	2.2	6.00	0.79	0.70	0.66	1.40	1.75	1.82	Recurrent pneumonia and (?) bronchiectasis
S. B. 6 yr.	19.10	1.0	6.48	—0.06	0.69	0.62	0.43	0.06	0.49	Recurrent pneumonia and (?) bronchiectasis
D. V. 10 mo.	6.77	1.0	5.47	0.23	—0.58	—0.23	1.44	0.88	....	Severe chronic pneumonia and bronchiectasis
D. F. 15 mo.	6.81	1.8	7.17	—0.44	—0.13	0.06	—0.47	0.06	—0.69	Chronic pneumonia
D. N. 1 mo.	2.52	1.5	4.46	—0.22	—0.04	—0.01	0.46	0.32	0.19	No pulmonary symptoms
D. N. 6 wk.	2.61	1.5	4.13	—0.18	0.25	0.51	0.14	....	1.02	No pulmonary symptoms
T. D. 4 mo.	3.45	1.5	3.50	0.35	0.49	0.49	0.93	0.99	0.66	No pulmonary symptoms
T. D. 4 mo.	3.31	1.5	4.46	—0.56	—0.33	—0.25	....	—0.46	—0.40	No pulmonary symptoms
T. D. 5 mo.	3.63	1.5	4.43	—0.08	—0.19	0.50	....	....	0.25	No pulmonary symptoms
T. D. 7 mo.	5.45	1.5	5.65	0.92	....	—0.39	....	....	—0.53	No pulmonary symptoms
J. G. 9 mo.	5.83	1.5	4.27	0.00	0.21	0.62	1.26	1.03	0.51	Severe chronic pneumonia and bronchiectasis
M. W. 5 mo.	3.75	1.5	5.29	0.70	0.34	0.33	....	....	—0.21	Mild chronic pneumonia
M. W. 5 mo.	4.12	1.5	5.87	—0.23	0.26	0.92	....	—0.18	0.24	Mild chronic pneumonia

A rise is always noted one-half hour after ingestion of the protein. In thirteen of the twenty-nine tests run in this group, the half-hour level represented the greatest elevation of amino nitrogen. In ten the greatest elevation occurred at one and one-fourth hours, in five at two and one-fourth to two and one-half hours and in only one was it delayed until three and one-fourth hours. In every case the amino nitrogen was elevated above 1 mg. per hundred cubic centimeters by the time the one and one-fourth hour specimen was obtained, even in the infant lacking a goodly portion of his small bowel.

GROUP 5. *Cystic Fibrosis of the Pancreas (table 5, chart 5).*—(As will be noted in the table, four of these curves were obtained after test meals varying from the usual 1.5 Gm. per kilogram, two with larger and two with smaller doses. We do not think this resulted in important

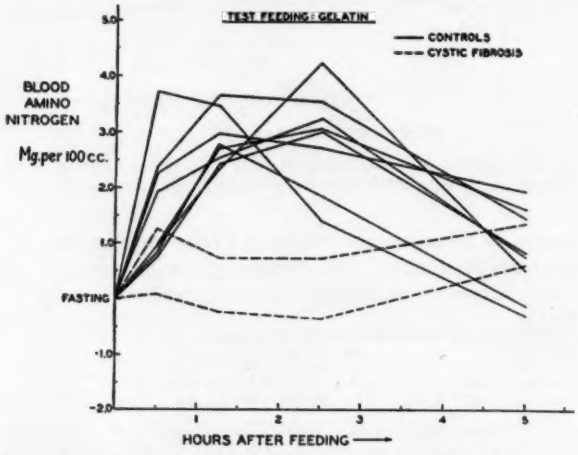

Chart 6.—Amino nitrogen absorption curves following ingestion of gelatin by infants with normal pancreatic function and with cystic fibrosis of the pancreas.

TABLE 6.—*Changes in Blood Amino Nitrogen Following Ingestion of Gelatin by Infants with Normal Pancreatic Function and with Cystic Fibrosis of the Pancreas*

Patient	Age	Weight, Kg.	Protein (Gelatin) Content of Test Feeding, Gm./Kg.	Blood Amino Nitrogen, Mg. per 100 Cc.					Clinical Group
				Fasting	½ Hr.	1¼ Hr.	2½ Hr.	5 Hr.	
K. B.	10 wk.	3.72	1.5	4.08*	0.92*	2.73	3.08*	1.63*	1
C. L.	2 yr.	7.80	1.5	4.86	2.29	2.98	2.74	1.96	2
M. G.	1 yr.	5.73	1.5	7.60	0.85	2.78	1.88	—0.11	4
S. A.	3 mo.	3.78	1.5	6.03	2.39	3.68	3.56	1.44	3
M. M.	1 yr.	5.06	1.5	5.96	0.77	2.44	3.01	0.81	2
V. R.	4 mo.	4.85	1.5	5.70	....	2.34	4.27	0.53	2
V. P.	6 mo.	4.60	1.5	6.07	1.92	2.56	3.17	0.78	2
E. D.	10 mo.	5.31	1.5	6.66	3.73	3.49	1.41	—0.30	4
D. N.	3 mo.	2.88	1.5	4.08	0.09	—0.21	—0.34	0.62	5
T. D.	8 mo.	6.02	1.5	5.43	1.29	0.76	0.76	1.39	5

* Venous blood determination.

differences in the curves obtained.) All curves in this group show a configuration very different from those for patients with normal pancreatic function in the other four groups. Nine of the thirteen show either no elevation or a drop in the blood amino nitrogen level one-half hour after the ingestion of the casein. In all of this group, the amino nitrogen was never elevated to 1.0 mg. per hundred cubic centimeters above the fasting level until three to three and one-fourth hours after the ingestion of protein. This phenomenon was noted even in the curve obtained after the ingestion by S. B. of 2.2 Gm. of protein per kilogram. Because this child weighed 19.1 Kg. (42 pounds), the test feeding was excessive, yet the configuration of the curve is much flatter than those for patients with normal pancreatic function. The general tendency of all the curves is either to run parallel to the fasting level throughout the five hour period or to show a slow rise toward the end of the period.

Test Feeding of Gelatin (table 6, chart 6).—As a group and when compared individually, the curves for infants with normal pancreatic function (solid lines) receiving this test meal are more elevated and the elevation more sustained than are those following a test meal of casein. While the curves also show individual variations, there is a greater tendency for them to fall into a definite pattern. The curves for the 2 patients with cystic fibrosis of the pancreas (dotted lines) are of quite different configuration but are not quite as flat as the curves after the meal of casein. There seems to be the same tendency to rise toward the end of the five hour period.

COMMENT

Test Feeding of Casein.—The curves for infants with normal pancreatic function given a test feeding of casein show considerable uniformity of elevation despite individual differences. Certainly they are more consistently elevated than would be expected of dextrose tolerance curves for a similar group of infants. The tendency of the curves of patients in all four groups with normal pancreatic function to show the same consistent rise indicates that infection, diarrhea, malnutrition and celiac disease have, in these infants at least, little or no influence on the production of amino acids from ingested protein. If one assumes that the presence of trypsin is necessary for this rise in blood amino nitrogen, the observation that, except in extreme marasmus, the duodenal content of trypsin is little affected by disease [20] correlates well with the uniformity of these curves. Several of the curves show

20. Andersen, D. H.: Pancreatic Enzymes in the Duodenal Juice in the Celiac Syndrome, Am. J. Dis. Child. **63**:643-658 (April) 1942. Farber, S.; Shwachman, H., and Maddock, C. L.: Pancreatic Function and Disease in Early Life: I. Pancreatic Enzyme Activity and the Celiac Syndrome, J. Clin. Investigation **22**:827-838 (Nov.) 1943.

irregularities. This has been noted in adults after test feeding of casein.[8] No explanation is attempted for these irregularities.

The results obtained from patients with cystic fibrosis of the pancreas contrast sharply with those from patients having normal pancreatic function. The general flattening, with the tendency to rise toward the end of the five hour period, makes this test of value in the diagnosis of this disorder. The failure of the blood amino nitrogen to rise above the fasting level, as seen in some of the curves, cannot be interpreted as indicating that these patients derive no benefit from dietary protein. Andersen [9] has shown that they do retain between 40 to 60 per cent of the ingested protein, the absolute amount retained varying directly with the intake of protein. In considering these absorption curves, it must be remembered that the fluctuations of amino nitrogen in the peripheral blood produced by ingestion of protein are buffered by the activity of the liver in storing and deaminizing amino acids brought to it by the portal system. If intestinal absorption of amino acids is slight, the liver may take up all of them, and no detectable change in the level of amino acids in the peripheral blood may be produced.

When one considers what is known of the physiology of digestion, it is remarkable that any protein whatever is retained by these patients. Ingested protein must be hydrolyzed to peptides before the combination of peptidases known as erepsin, produced by the intestinal wall, can act to split it into its constituent amino acids. Trypsin and associated proteolytic enzymes produced by the pancreas carry almost the entire burden of hydrolysis to the peptide stage. The proteolytic pancreatic enzymes are thus indispensable if digestion of protein is to be adequate. Other enzymes may substitute for them to a slight extent. Pepsin, in association with the hydrochloric acid of the stomach, can hydrolyze some protein to the peptide or even to the amino acid stage.[21] However, it is only by prolonged action in vitro that this can be demonstrated. The short time that food remains in the stomach militates against peptic digestion's accounting for any extensive hydrolysis. Bacterial action may account for some hydrolysis of protein. Absorption of native proteins, proteoses and peptones undoubtedly does occur, but probably not to the extent of 40 to 60 per cent of the protein intake. To account, then, for this retention of protein demonstrated by Andersen and for the terminal rise of the blood amino nitrogen level noted in some of the curves, we have recourse only to the possibility that trypsin is produced by these patients in small amounts. By viscometric methods of trypsin assay, small amounts have been demonstrated in some [20]; this may account, in part, for the variable nature of the clinical course found with this disease.

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21. Calvery, H. O.: Crystalline Egg Albumin: II. The Fractionation of Peptic Hydrolysis Products, J. Biol. Chem. **112**:171-174 (Dec.) 1935.

Test Feeding of Gelatin.—The greater elevation and regularity of the curves in patients with normal pancreatic function given this test feeding as compared with the results after a feeding of casein is readily apparent. Although 1 of the 2 patients with cystic fibrosis of the pancreas given this test feeding showed greater elevation of amino nitrogen than did any similar patients after feeding of casein, the discrepancy between the abnormal and the normal is great. Only a few tests were done using gelatin because it was not discovered until nearly the end of the period of time devoted to the study that the elevation of the amino nitrogen level following ingestion of gelatin was greater than that following ingestion of casein. If further work on these two groups of patients shows similar curves, it would appear that for purposes of diagnosis a test feeding of gelatin is superior to one of casein. Because of the regularity of the elevation, the number of specimens of blood taken might be reduced and enough information might still be obtained to aid greatly in ruling in or out a diagnosis of pancreatic deficiency.

The greater elevation of blood amino nitrogen following feeding of gelatin as compared with feeding of casein has been noted previously in the experimental animal.[22] It has been attributed to the greater aminoacetic acid and alanine content of gelatin. In the experimental animal these two amino acids give greater and more prolonged amino-acidemia than do any of the others when fed in equal amounts.[23] Casein, on the other hand, contains only small amounts of aminoacetic acid and alanine and is relatively high in glutamic and hydroxyglutamic acid, two amino acids which produce little or no elevation of blood amino nitrogen following ingestion.

II. CHANGES IN THE AMINO NITROGEN CONTENT OF THE PERIPHERAL BLOOD FOLLOWING INGESTION OF A CASEIN HYDROLYSATE AND OF CASEIN AND PANCREATIN BY PATIENTS WITH AND WITHOUT PANCREATIC DEFICIENCY

An acid hydrolysate of casein (Parenamine [13]) was tested in patients without apparent pancreatic disease (as in groups 1 to 4 previously

22. Kratzer, F. H.: Amino Acid Absorption and Utilization in the Chick, J. Biol. Chem. **153**:237-247 (April) 1944.

23. Séth, T. N., and Luck, J. M.: The Relation Between the Metabolism and Specific Dynamic Action of Amino Acids, Biochem. J. **19**:366-376, 1925. Luck, J. M.: The Estimation of Amino Acid Nitrogen in Animal Tissues, J. Biol. Chem. **77**:1-12 (April) 1928. Johnston, M. W., and Lewis, H. B.: Comparative Studies of the Metabolism of Amino Acids: I. Changes in the Non-Protein Nitrogenous Constituents of the Blood Following Administration of Amino Acids, ibid. **78**:67-82 (June) 1928. Kratzer.[22]

mentioned) and in patients with cystic fibrosis of the pancreas (group 5.) Casein with pancreatin was used only for patients with cystic fibrosis of the pancreas.

RESULTS

Test Feeding of a Casein Hydrolysate to Patients with Normal Pancreatic Function (table 7, chart 7).—If a mean curve were drawn from the data here, it would be considerably more elevated and the

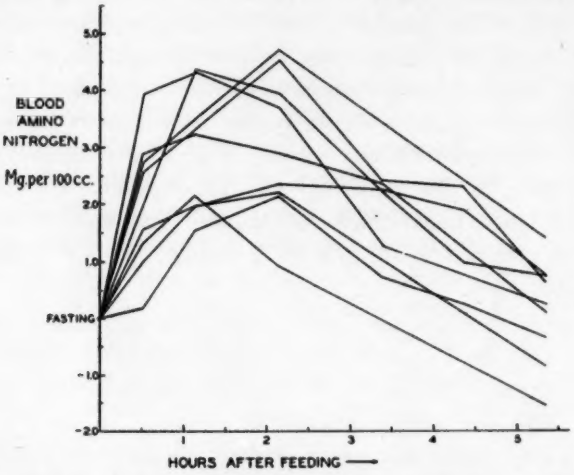

Chart 7.—Amino nitrogen absorption curves following ingestion of a casein hydrolysate by infants with normal pancreatin function.

TABLE 7.—*Changes in Blood Amino Nitrogen Following Ingestion of a Casein Hydrolysate by Infants with Normal Pancreatic Function*

Patient	Age	Casein Equivalent of Hydrolysate Test Weight, Kg.	Feeding, Gm./Kg.	Blood Amino Nitrogen, Mg. per 100 Cc. Fasting	½ Hr.	1 to 1¼ Hr.	2 to 2¼ Hr.	3¼ to 3½ Hr.	4¼ to 4½ Hr.	5¼ to 5½ Hr.	Clinical Group
W. J.	3 wk.	3.18	1.5	4.68	2.59	....	4.56	2.42	2.33	0.65	1
B. G.	10 mo.	4.61	1.5	7.30	1.34	2.16	0.95	—0.07	....	1.52	2
S. D.	6 mo.	4.37	1.5	4.22	3.94	4.31	3.73	1.30	0.75	0.29	2
C. E.	4 mo.	4.32	1.5	4.13	....	4.36	3.96	2.22	0.99	0.76	2
D. L.	8 mo.	5.51	1.5	4.21	2.74	....	4.71	....	....	1.40	2
C. S.	8 mo.	6.64	1.5	4.59	2.90	3.23	2.90	2.38	....	0.09	3
G. C.	10 mo.	5.11	1.5	4.40	1.01	1.99	2.39	2.26	1.92	0.75	3
M. H.	18 mo.	6.25	1.5	5.61	0.19	1.58	2.17	0.75	0.27	—0.32	3
M. G.	1 yr.	5.80	1.5	6.56	1.57	1.98	2.21	....	....	0.84	4

peak of absorption would be more delayed than would such a curve drawn from the data following test feedings of intact casein (tables 1, 2, 3 and 4). As before, there is considerable variation in the curves. The curve reaching a low peak at one and one-fourth hours and falling away rapidly thereafter is that of patient B. G., who had had the resection of the ileum as mentioned previously. Again, we believe.

his diminished absorptive surface is illustrated by the curve obtained. In all other cases the heights attained by the curves did not correlate well with any clinical observations.

Patients with Cystic Fibrosis of the Pancreas (table 8, chart 8).—These curves show essentially the same configuration as those for patients with no pancreatic deficiency. Two of them, those of D. F. and S. B., were obtained following the administration of the casein hydrolysate masked with a flavored gelatin preparation as described previously.

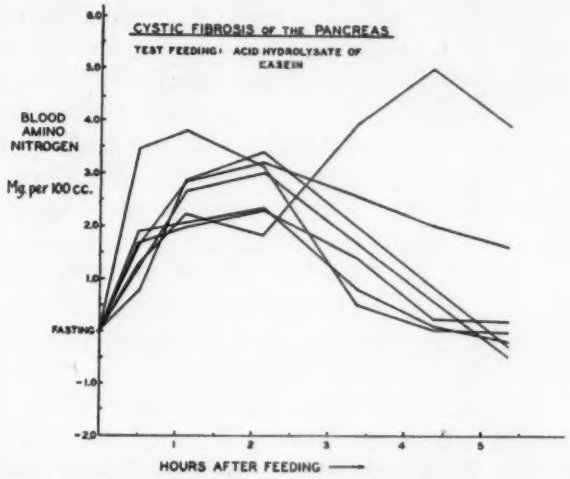

Chart 8.—Amino nitrogen absorption curves following ingestion of a casein hydrolysate by infants and children with cystic fibrosis of the pancreas (group 5).

TABLE 8.—*Changes in Blood Amino Nitrogen Following Ingestion of a Casein Hydrolysate by Infants and Children with Cystic Fibrosis of the Pancreas (Group 5)*

Patient and Age	Weight, Kg.	Casein Equivalent of Hydrolysate Test Feeding, Gm./Kg.	Blood Amino Nitrogen, Mg. per 100 Cc.							Comments
			Fasting	½ Hr.	1 to 1¼ Hr.	2 to 2¼ Hr.	3¼ to 3½ Hr.	4¼ to 4½ Hr.	5¼ to 5½ Hr.	
D. F. 15 mo.	6.98	1.75	6.66	1.29	2.26	1.84	8.98	5.02	3.98	Chronic pneumonia
S. B. 6 yr.	19.10	1.0	5.88	1.68	2.89	3.25	2.61	2.07	1.68	Recurrent pneumonia (?); bronchiectasis
D. V. 10 mo.	6.59	1.0	5.47	1.70	2.02	2.35	1.44	0.29	0.23	Severe chronic pneumonia and bronchiectasis
D. N. 5 wk.	2.46	1.5	4.46	3.50	3.83	3.17	0.55	0.08	0.02	No pulmonary symptoms
T. D. 4 mo.	3.23	1.5	4.92	0.78	2.90	3.44	....	....	—0.24	No pulmonary symptoms
J. G. 9 mo.	5.22	1.5	4.98	1.93	....	2.39	0.84	0.12	—0.17	Severe chronic pneumonia and bronchiectasis
M. W. 6 mo.	4.31	1.5	7.39	1.21	2.70	3.04	....	....	—0.45	Mild chronic pneumonia

Both show as great an elevation as the others which were obtained by simply mixing the hydrolysate with water and giving it by gavage. No explanation can be given for the sudden terminal rise in the case of D. F. It is interesting that the two lowest curves in this group were obtained for patients with severe pulmonary involvement (D. V. and J. G.), both of whom died within one month after the tests were done.

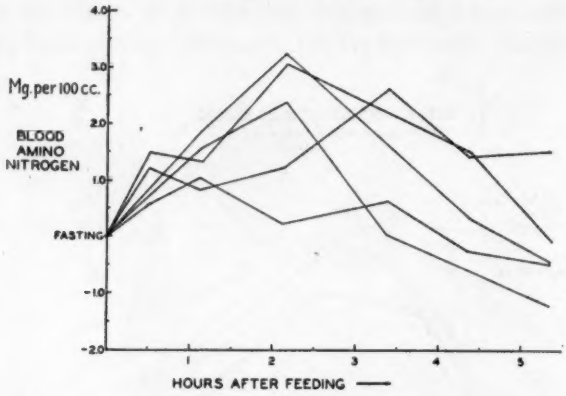

Chart 9.—Amino nitrogen absorption curves following ingestion of casein with 0.65 Gm. pancreatin by infants and children with cystic fibrosis of the pancreas (group 5).

TABLE 9.—*Changes in Blood Amino Nitrogen Following Ingestion of Casein with 0.65 Gm. of Pancreatin in Infants and Children with Cystic Fibrosis of the Pancreas (Group 5)*

Patient and Age	Weight, Kg.	Protein (Casein) Content of Test Feeding, Gm./Kg.	Blood Amino Nitrogen, Mg. per 100 Cc. Fasting	½ Hr.	1 to 1¼ Hr.	2 to 2¼ Hr.	3¼ to 3½ Hr.	4¼ to 4½ Hr.	5¼ to 5½ Hr.	Comments
D. F. 14 mo.	6.98	1.75	7.69	0.67	1.59	2.41	0.06	....	—1.21	Chronic pneumonia
S. B. 6 yr.	19.10	1.0	6.23	1.20	0.81	1.13	2.62	1.46	1.52	Recurrent pneumonia and (?) bronchiectasis
D. V. 9 mo.	6.76	1.0	6.66	0.57	1.03	0.25	0.64	—0.24	—0.49	Severe chronic pneumonia and bronchiectasis
T. D. 8 mo.	6.16	1.5	5.77	....	1.86	3.24	....	0.32	0.44	No pulmonary symptoms
M. W. 6 mo.	4.37	1.5	5.93*	1.49*	1.34*	3.05*	....	1.52*	—0.06*	Mild chronic pneumonia

* Venous blood determination.

Test Feeding of Casein and Pancreatin (table 9, chart 9).—All patients given this feeding had cystic fibrosis of the pancreas. A mean curve drawn from the data obtained here would not be as high as one obtained from data after feeding of the casein hydrolysate (table 8). The curves are also not as regular as those made after feeding of the casein hydrolysate. In most cases, however, the elevation is strikingly greater

than when casein is given without pancreatin to these patients (table 5, chart 5). The one curve in which the elevation is not great was obtained for D. V., who had severe pulmonary involvement. It is difficult to see how this would so greatly influence the curve here and yet so little influence it when the casein hydrolysate was given (chart 8).

COMMENT

The greater elevation of amino nitrogen following administration of a casein hydrolysate as compared with that following administration of an equivalent amount of casein (in terms of nitrogen content) is extremely apparent in all cases studied, but the difference is especially striking in patients with pancreatic deficiency. It would appear that infants with pancreatic deficiency derive as much benefit from the casein hydrolysate as do those with normal pancreatic function. To this extent predigestion of protein thus bypasses the barrier to digestion of protein set up by the absence of trypsin. The curves help to confirm the clinical and metabolic evidence of the efficacy of this form of therapy in this disease.

The greater elevation of amino nitrogen observed in the persons with normal pancreatic function given the casein hydrolysate as compared with the elevation following administration of nonhydrolyzed casein has also been observed in the experimental animal.[22] We believe it can be accounted for. Hydrolysis of intact casein may continue at a slow rate for some time beyond the five and one-fourth hour test period, and absorption of the resultant amino acids causes little elevation of the peripheral blood amino nitrogen level owing to the buffering effect of the liver. The curves drawn after a test meal of the casein hydrolysate appear almost to encompass the period of absorption of amino acids in their five and one-fourth hour span. It has also been suggested [22] that the amino nitrogen elevation is less following a protein meal because of absorption of greater quantities of amino acid complexes, which would be only partially detected,[18] if at all, by the method of blood analysis used here. If they were detected, the resultant increase of amino nitrogen would not be in proportion to their metabolic value.

Substitution therapy in the form of administration of pancreatin would also seem to circumvent the defect in the digestion of protein produced by the absence of trypsin and to result in greater absorption of amino acids. The failure of the curves to rise to the same extent as those obtained after the feeding of casein hydrolysate may again be due to the absorption of undetected amino acid complexes.

Both predigested casein and pancreatin have their distinct advantages in therapy. Pancreatin has two advantages not found with a casein hydrolysate. It is much easier to ingest, a factor of great importance with older children. It also contains variable amounts of lipase, which

may allow slightly increased tolerance for fat and aid in the absorption of fat-soluble vitamins. However, in young infants up to the age of 18 months, a casein hydrolysate has much to offer. When combined with skimmed milk and added carbohydrate, the majority of infants with this disease will take it with seeming relish despite the strong flavor. One infant in the group on whom these studies were done was possibly intolerant to it, diarrhea developing when the hydrolysate was given in adequate amount, although its specificity in causing the diarrhea was never proved to our complete satisfaction. It has been used with 4 of the others with considerable success, up to 4 Gm. (dry weight) per pound (453 Gm.) of body weight being used without ill effect. For older children it may be incorporated in a flavored gelatin preparation as described previously in this paper and in this form is taken well in most cases. As much as 30 to 45 Gm. may be incorporated in a pint (0.5 liter) of such a gelatin preparation, adding (with the carbohydrate content) materially to the intake of "available" calories. Because these children supposedly have normal ability to hydrolyze the polypeptides, which are present in significant amounts in hydrolysate preparations, one can assume that all the hydrolysate intake can be utilized. Thus, by using hydrolysates, a calculated protein requirement can be accurately and dependably met. On the other hand, without balance studies, the protein retention of children receiving pancreatin cannot be definitely determined. There is also some difficulty in administering pancreatin to extremely young infants not yet taking solid foods.

It would seem essential that use be made of one or both of these preparations to satisfy the protein requirement of these patients.

SUMMARY

The fluctuation of peripheral blood amino nitrogen following ingestion of casein,[10] gelatin,[12] casein with pancreatin [11] and an acid hydrolysate of casein [13] has been studied. The studies were done on 4 normal infants, 21 sick infants with no pancreatic disease and 7 infants and children with cystic fibrosis of the pancreas.

Within one and one-fourth hours after ingestion of 1.5 Gm. of casein [10] per kilogram of body weight, there was an increase in blood amino nitrogen of 1.0 mg. per hundred cubic centimeters or greater in all infants studied who had normal pancreatic function. The configuration of the amino nitrogen curve could not be correlated with disease for these patients.

Within one and one-fourth hours after the ingestion of a similar amount (equivalent in nitrogen content) of gelatin,[12] the blood amino nitrogen rose more than 2.0 mg. per hundred cubic centimeters in patients with normal pancreatic function. The amino nitrogen curve is

more regular and more sustained than is that obtained after the ingestion of casein.

After the ingestion of a similar amount of casein or gelatin by infants or children with cystic fibrosis of the pancreas, the blood amino nitrogen remained close to the fasting level for a considerable period, occasionally showing some tendency to rise after three to five hours. This difference in response to a protein meal between infants and children with normal pancreatic function and those with cystic fibrosis of the pancreas was of sufficient constancy and magnitude in the patients studied to constitute a specific diagnostic test for this disorder. In our patients there were no discrepancies between the occurrence of a characteristic flat curve and the absence of trypsin in the duodenal juice, nor between the observation of a characteristic elevation of the curve and the presence of normal pancreatic juice,

The elevation of blood amino nitrogen following ingestion of an acid hydrolysate of casein [13] was found to be greater in all patients than that following ingestion of an amount of intact casein having the same nitrogen content.

The elevation of blood amino nitrogen following ingestion of the casein hydrolysate by infants and children with cystic fibrosis of the pancreas was similar to the elevation following a similar feeding in infants with normal pancreatic function. This confirms the clinical and metabolic evidence of the therapeutic value of substituting hydrolyzed protein for intact protein in the diets of children with cystic fibrosis of the pancreas.

Simultaneous administration of 0.65 Gm. of pancreatin (enteric-coated granules [11]) with the dose of intact casein to children with cystic fibrosis of the pancreas produced in most cases considerably greater elevation of blood amino nitrogen than does intact casein given alone. This likewise confirms the evidence for the value of this form of therapy in children with cystic fibrosis of the pancreas.

CRITERIA FOR RECOGNITION OF NEUROSES IN CHILDREN

A Guide for the Pediatrician

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NEW YORK

RECOGNITION of the value of psychiatric treatment of children is spreading rapidly, but the selection of cases for psychiatric care is still determined more often by the complaints of parents than by objective criteria. This paper presents a developmental approach to the recognition of neurotic disorders in childhood.

Thanks to the contributions of the psychometric and developmental branches of psychology, the well read pediatrician, equipped with books by Bühler,[1] Gesell,[2] Kulmann[3] and others, can detect a child who is subnormal in mental development. But what appears like mental subnormality may be a symptom of disturbed instinctual development. To recognize this symptom for what it is and to recognize other neurotic symptoms that may be present, it is necessary to know the normal progression of instinctual life. The recognized sequence of instinctual development is from the oral level to the anal level, the phallic level, the latency period and the genital level.

DEVELOPMENTAL SEQUENCE

Oral Level.—This period begins at birth and lasts until the child is approximately 18 months old. During this period, the mouth leads in the infant's adaptation to the outside world. He can be said to taste his way through life. The mouth is his organ of pleasure and aggression. The normal child of this period enjoys his food and explores his environment actively with his mouth: first, his own body and that of his mother and then everything within reach. It follows that thumb sucking, biting and putting things in the mouth are normal activities for this age. Temperamentally the oral child is insatiable, impatient and demanding. He reaches for the moon, as the saying goes. The well child who does not enjoy his food, who is lethargic and uninterested in the world about him, and who, even after the first year, is more pre-

1. Bühler, C.: The First Year of Life, translated by P. Greenberg and R. Ripin, New York, The John Day Company, Inc., 1930.

2. Gesell, A. L.: Mental Growth of Preschool Child, New York, The Macmillan Company, 1925.

3. Kulmann, F.: Revision of Binet-Simon System for Measuring Intelligence of Children, J. Psychoasthenics, 1912, Monograph supp. 5, no. 1.

occupied with his own body pleasure, such as thumb sucking, masturbation, rocking and head banging than he is responsive to his mother and others close to him—such a child reveals evidence of some interference with normal functioning. The pediatrician should be on the lookout for reasons other than medical to explain the state, assuming these have been ruled out. Whether he applies his own psychiatric stethoscope or refers the child to a psychiatrist is a matter related to his training and experience. In any case, it must be determined in what ways the environment is frustrating or traumatizing: Are normal biting and sucking experiences interfered with? Is the child left alone too much? Is he handled too much and with anxiety? It is as important to grasp the principle of individual differences in libidinal as in physical and mental endowment. Applied to the child at the oral level, this means that certain children have stronger oral needs than others. Means should be found to satisfy these constructively, as by supplying a variety of objects to suck and bite.

Anal Stage.—This level probably starts earlier, lasts longer and is more striking, the earlier training begins and the more exacting it is. During this period, emotional development is organized around the anal zone. The child's impressions and phantasies of the outside world are related to the experience of evacuation and to the role of adults in the experience. Like the mouth, the anus is an organ of pleasure and aggression. Normally, the young child is as interested in his excreta as in his body. Nevertheless, he is quite ready to part with the interest, in conformity with the training schedule, in exchange for the love of his mother or nurse. In their book "Infants without Families," Anna Freud and D. Burlingham [4] have confirmed the theory that institutional children are retarded in habit training but that they respond with dramatic promptness as soon as they are organized around a teacher-mother who assumes full responsibility for their training. There is evidence from all sources that children resent early and rigorous training, even if they comply. But the child who resists training after 2, who wets and soils himself after getting up from the chamber, who holds back his excreta, who is chronically constipated, who smears himself with his feces or whose habit training breaks down periodically—such a child shows indications of a neurosis or of neurotic handling. Such children may later become unduly clean and orderly. This change is known as a reaction-formation in defense of their anal erotism. The alert pediatrician will spot these children and treat them not with suppositories, cathartics, enemas or wishful thinking about outgrowing the symptoms, but with education of the parent. If he is reasonably sure that the mother's

4. Freud, A., and Burlingham, D.: Infants Without Families, New York, International Universities Press, Inc., 1944.

standards have not been too high, that anal interests have been tolerated and substitute outlets provided, such as paints, clay, sand and water play, and that the environment has not been abnormally frustrating or traumatizing, then he will know that such a child needs psychiatric care.

Phallic Phase.—This level coincides more or less with the oedipus experience; that is, it appears from 3 to 5 years. Though the child may have observed differences between male and female before, he now becomes keenly aware of his genitals and of sex differences. For both sexes this leads to more or less acute castration anxiety, in the girl felt as penis envy. It also lends momentum to the oedipus relationship. The boy in his pride of miniature manhood turns passionately toward the mother, regarding his father as his rival. The girl, under the smart of penis envy, turns to the father, yearning for everything the mother gets from him and at the same time regarding the mother as her rival. Both boys and girls have rich phantasies about marital intimacy but do not as yet have a true conception of intercourse. Not for a moment must it be supposed that the child normally hates the parent of the same sex. The little boy admires, fears, hates and loves his father. The girl's feelings for the mother are even more complex, because her infantile attachment to the mother is stronger than the boy's infantile attachment to the father. Temperamentally the phallic-oedipus child is exceedingly rich and complex, with many of the traits of a lover. Under such emotional impact family relationships easily lend themselves to distortion. Typical distortions are persistent passive-feminine identification in the boy and masculine identification in the girl, extreme anxiety, expressed in night terrors and undue dependence on the mother, vigilance of her and submissiveness to her, these states often alternating with aggression against her. Enuresis is common during this period and has many determinants, but it is rarely "elevated" to the status of a symptom before the latency period. To check on indications of neurosis during the phallic-oedipus period, the psychiatrically minded pediatrician will explore parent-child relationships, and he will be suspicious of the particularly good child of 3 to 5, especially if it is a boy.

Latency Period.—This level marks a decrease in infantile sex feelings, partly for biologic reasons and partly as a result of inevitable oedipus frustrations. Normally during the period of latency the child yields readily to sublimations, i. e., substitute gratifications such as achievement at school and development of talents and special aptitudes. He goes in passionately for competitive and warlike games, for hobbies and for outside friendships. Not only have the passionate feelings of love and hate, so freely expressed during the phallic-oedipus period, subsided, but they have shifted from the parents to mates the child's age. If sexual feelings remain too strong and threatening, however, the child throws up

defense mechanisms. All children (and adults) resort to defense mechanisms to quiet anxiety. If anxiety is excessive, the defenses are overworked and the result is interference with development. A. Freud's book "The Ego and The Mechanisms of Defense" [5] gives a remarkably clear picture of defense mechanisms at work. To evaluate defense mechanisms in terms of the balance between ego and libido is to understand neurosis. But the more conspicuous indications of neurosis in the child during the period of latency are disturbances in the learning process, not accounted for by intellectual capacity, feminine identification in the boy and masculine identification in the girl, tics, compulsions, lying, stealing, fears, phobias, enuresis and tantrums. If tantrums do not subside during this period, then they become more violent. They should be interpreted either as attempts to break the bonds of oedipal involvement or as an invitation to be beaten, based on a masochistic distortion of sexual intercourse.

Genital Phase.—This brings the child to the genital phase, i. e., to prepuberty. An increase in glandular activity stimulates sexual strivings. The balance in favor of the ego, so precariously established during the latency period, tips now in favor of libido. What is more, the balance is unstable throughout adolescence, tipping now with the weight of ego strivings and again with the weight of libidinal wishes, giving the familiar picture of the adolescent: a mixture of adult and child. Nevertheless, this bespeaks a healthy fluidity between instinctual demands and ego controls. The sexual reawakening at puberty recapitulates the feelings of the oedipus period. But the recapitulation should be brief and should serve as a bridge to heterosexual relationships. The young adolescent who does not show some interest in the opposite sex, whose social life is restricted, who continues in his passive-submissive role or assumes it (masculine-aggressive for the girl) and whose swings from infantile behavior to adult-like demands are extreme or who shows emotional rigidity—such an adolescent shows a neurotic picture and is in need of psychiatric care.

COMMENT AND CONCLUSION

The course of libidinal development, as described, should be seen as a sequence, making allowance for overlapping. One developmental stage is not left completely behind before the next one is reached. A child of 4 in the phallic phase has traces of oral and anal interests, but the phallic features predominate. It can even be argued that no developmental stage is left completely behind. Behold the smokers! Complete oral and anal satisfaction is not attained in our culture. This leaves a

5. Freud, A.: The Ego and the Mechanisms of Defence, London, Hogarth Press, 1937.

residue of points of frustration and fixation. But two ingredients do not make a neurosis. The over-all criterion of a child neurosis given by A. Freud in her paper "Indications for Child Analysis" [6] helps one to see symptoms in perspective. "There is only one factor in childhood of such central importance that its impairment through a neurosis calls for immediate action: namely, the child's ability to develop, not to remain fixated at some stage of development before the maturation process has been concluded."

I have tried to show that the child's ability to develop depends, on the one hand, on his endopsychic forces, and on the other, on environmental pressures. These are complementary and interacting. To judge whether a child is capable of spontaneous recovery or needs psychiatric help, it is essential to evaluate his developmental history, which should be all-inclusive, against the environment in which he lives. He stands a better chance of recovery in certain environments than in others. Some environmental factors are known to be traumatizing. They are in the order of effect: disturbed relations between parents, decided reversals in parental types, i. e., passive-submissive father and aggressive mother; rejecting or overprotecting parents and striking differences in endowment of siblings. The adopted child and the physically handicapped child are also susceptible to neurotic disturbance.

If this paper helps pediatricians to recognize neurotic disturbances in children, it will have served its purpose. The severity of the disturbance can be judged only by a psychiatric examination. The program of treatment, too, should be based on such an examination. If the child is under pediatric care, the psychiatric treatment should be carried out in collaboration with the pediatrician.

105 East Thirty-Eighth Street.

6. Freud, A.: Indications for Child Analysis, in Freud, A.; Hartman, H., and Kris, E.: The Psychoanalytic Study of the Child, New York, International Universities Press, Inc., 1945.

TREATMENT OF IMPETIGO NEONATORUM WITH MINIMAL DOSES OF PENICILLIN

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THIS report is a brief record of our experience in treating impetigo neonatorum with small doses of penicillin. We feel that it is worth recording because the method materially simplified the treatment and technics in the nursery of newly born infants.

Between Jan. 1, 1944 and May 15, 1945, 10 infants with impetigo were seen among the newly born babies in the obstetric nursery at St. Mary's Hospital, Rochester, Minn. The eruptions occurred in spite of the fact that no baths or inunctions with oil were given to any of the babies during their stay in the hospital. While this is not a large number, each instance seriously complicated the nursing care in our ward, already understaffed and overbusy.

Under our previous routine, each baby as soon as the diagnosis was made was moved to an isolation ward, where he was kept until all symptoms had disappeared. As a rule, such patients remained in isolation until dismissal, a matter of several days.

Beginning in January 1944 all babies who had impetigo neonatorum received chemotherapy in the form of intramuscular injections of penicillin. The first patients were given 2,500 units in 1 cc. of isotonic solution of sodium chloride every three hours. Since healing occurred before the end of twenty-four hours, the dose was quickly reduced until in 3 cases a total of only 5,000 units per patient was given. This dose apparently caused definite healing within twenty-four hours, with almost complete clearing of the skin immediately thereafter. Local treatment when given consisted of applying an antiseptic solution after breaking the blisters and dusting with a powder containing 10 per cent mild mercurous chloride U. S. P.

REPORT OF CASES

CASE 1.—The patient was a full term baby boy with a birth weight of 3,750 Gm. On the fifth postnatal day pustular lesions were seen in the right axilla, extending to the right side of the thorax. A diagnosis of impetigo neonatorum was made, and 5,000 units of penicillin sodium in 1 cc. of isotonic solution of sodium chloride

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was given intramuscularly. Twenty-four hours later the lesions were healing well, and no new blisters were seen.

CASE 2.—The patient was a full term baby boy whose birth weight was 3,710 Gm. On the fourth day numerous superficial pustular lesions were seen in both axillas and extending onto the thorax. A diagnosis of impetigo was made. Five thousand units of penicillin sodium in 1 cc. of isotonic solution of sodium chloride was given intramuscularly. Healing was in progress within twenty-four hours and was complete within three days.

CASE 3.—The patient was a full term baby boy with a birth weight of 3,460 Gm. A few pustular lesions were seen on the third postnatal day in both axillas and on the thorax. A diagnosis of impetigo was made. Two doses of 2,500 units of penicillin sodium, each in 1 cc. of isotonic solution of sodium chloride, were given intramuscularly at a three hour interval. The lesions were healing at twenty-four hours and had completely disappeared within three days.

Although healing took place rapidly when a total dose of 5,000 units was given, in order to err on the safe side, the routine treatment now given such children consists of two doses of 5,000 units each at a three hour interval as soon as the diagnosis is made. These babies are returned to the nursery with the other children within thirty-six hours of the beginning of treatment, which obviates considerable nursing care and the use of prolonged isolation. No spread to other babies has occurred.

SUMMARY

In 10 cases impetigo was treated with intramuscularly administered penicillin. A total dose of 5,000 units was seen to cause prompt healing of lesions. The routine therapy that we are now using consists of immediate isolation and two doses of 5,000 units of penicillin each at a three hour interval. Local treatment may or may not be used. The child is returned to the ward within thirty-six hours.

CLINICAL APPLICATIONS OF CHICK EMBRYO CULTURES

(I) Primary Diagnosis of Meningitis and Study of Spinal Fluid in Meningococcemia Without Meningitis; (II) In Vivo Streptomycin Sensitivity Test

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I. PRIMARY DIAGNOSIS OF MENINGITIS AND STUDY OF SPINAL FLUID IN MENINGOCOCCEMIA WITHOUT MENINGITIS

THE PRINCIPAL aim of clinical bacteriology is the rapid and accurate identification of pathogenic organisms so that the clinician may employ suitable specific therapeutic measures at the earliest moment. There have been innumerable attempts by bacteriologists to improve on basic culture mediums by devising modifications of the chemical composition and changes in the oxygen tension of the mediums in order to insure the most rapid and constant bacterial growth. The developing chick embryo as a culture according to the Goodpasture technic has been used by us as an aid in a variety of clinical problems, among them the etiologic diagnosis of purulent meningitis, the study of spinal fluid in early meningococcemia without meningitis and the serial study of empyema fluid. We have also employed a modification of this technic for an in vivo test of streptomycin sensitivity.

Rous and Murphy [1] introduced the chick embryo as a culture medium, and Goodpasture and his associates [2] were pioneers in its use for the

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1. Rous, P., and Murphy, J. B.: Tumor Implantations in the Developing Embryo: Experiments with a Transmissible Sarcoma of the Fowl, J. A. M. A. **56**:741 (March 11) 1911.

2. Woodruff, A. M., and Goodpasture, E. W.: The Susceptibility of the Chorio-Allantoic Membrane of Chick Embryos to the Infection with the Fowl-Pox Virus, Am. J. Path. **7**:209, 1931. Goodpasture, E. W.: Use of Embryo Chick in Investigation of Certain Pathological Problems, South. M. J. **26**:418, 1933. Goodpasture, E. W., and Buddingh, G. J.: The Preparation of Antismallpox

(Footnote continued on next page)

study of bacterial and virus pathogenesis. Their extensive studies and those of Buddingh [3] and others [4] have shown that this ready-made, sterile and inexpensive medium provides a sensitive pabulum for even the most delicate bacteria. Blattner, Heys and Hartmann [5] applied the Goodpasture technic to the culture of spinal fluid in meningitis, and they frequently were able to demonstrate viable bacteria when routine cultures already had become negative after therapy.

In our study, examinations of spinal fluid were made at the time of entry for over 100 patients with suspected meningitis, poliomyelitis or encephalitis, and the cultures revealed purulent meningitis in 51 of these patients. All fluids were cultured by routine methods on blood agar, Avery's broth and Loeffler's medium for use in slants; agar plates were incubated under reduced oxygen tension as indicated. Simultaneously, each spinal fluid was dropped on the chorioallantoic membrane of two chick embryos. The technic used in this study was Burnet's modification [6] and is described in detail.

METHOD

Fertile eggs, incubated at 37.5 to 38.5 C. and turned daily during the period of incubation, were candled between the sixth and the twelfth day to determine the viability of the embryo. In the eggs having viable embryos, the position of the air sac also was determined, and pencil marks were made on the shell over the embryo and over the air sac pole of the egg. A rotating carborundum disk on a hand drill was used to cut a small square, approximately 1 sq. cm. in size, in the shell over the embryo. A single small slit was made at the air sac pole. Next, a scalpel or blade was inserted through the single slit, and the shell membrane over

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4. Morrow, G., and Berry, G. P.: The Cultivation of Neisseria Gonorrhoeae on the Chorio-Allantoic Membrane of the Chick Embryo and the Use of This Technic for the Study of Sulfanilamide, J. Bact. **36**:280, 1938. Hill, J. H., and Pitts, A. C.: The Growth of Neisseria Gonorrhoeae on the Chorio-Allantoic Membrane of the Chick Embryo, J. Urol. **41**:81, 1939. Bang, F.: Experimental Gonococcus Infection of the Chick Embryo, J. Exper. Med. **74**:213, 1941. Weil, A. J., and Gall, L. S.: Chemotherapeutic Testing with Sodium Sulfathiazole in the Developing Chick Embryo, J. Infect. Dis. **69**:97, 1941.

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6. Burnet, F. M.: Influenza Virus Infections of the Chick Embryo Lung, Brit. J. Exper. Path. **21**:147, 1940.

the air sac was pierced. The square overlying the embryo was picked off without injuring the tough shell membrane. By gentle pressure with a scalpel at one side of the square, a small break was made in the membrane, and by applying slight suction with a rubber bulb at the opening over the air sac, the underlying vascular chorioallantoic membrane could be seen to fall away from the shell membrane. The shell membrane was then picked off with a forceps. Instead of using suction over the air sac, a drop of sterile saline solution could be placed on the shell membrane, and then a small nick could be made in it with a fine needle. This allowed the solution to spread between the chorioallantoic membrane and the shell membrane and separated the two. The materials to be tested (spinal fluid, pleural fluid, etc.) were dropped directly on top of the chorioallantoic membrane. The window margins then were rimmed with a melted paraffin–petrolatum mixture (in equal parts), and the window was sealed with a cover glass. The eggs were returned to the incubator and examined at varying intervals.

The volume of inoculum varied between 0.1 and 2 cc. In several instances, especially during the course of chemotherapy, injection of a larger volume of spinal fluid was followed by positive cultures when small amounts had failed to produce them (table 1).

TABLE 1.—*Effect of the Various Volumes of Spinal Fluid Injected in the Chick Embryo Method of Culture*

	Spinal Fluid					
		Volume				
Patient	Cell Count	0.1 Cc.	0.5 Cc.	1.0 Cc.	2.0 Cc.	Organism
S. B.	310	No growth	No growth	++++	++++	Meningococcus
M. G.	900	No growth	No growth	++++	++++	Pneumococcus (type 34)
A. G.	70	No growth	No growth	No growth	++++	Meningococcus
S. L.	1,442	No growth	No growth	No growth	++++	Meningococcus

The first examination was made six to seven hours after the inoculation. The cover slip was removed, the chorioallantoic membrane was gently touched with a sterile platinum loop, the cover slip was replaced and the material obtained dyed with Gram's stain to determine the presence of bacteria. If the result of the first examination was positive, subcultures on blood agar and brain broth were made, and in the case of a presumptive microscopic identification of pneumococci and H. influenzae, direct typing was possible. When no organisms could be seen, the egg was reincubated and examined again after twenty-four and forty-eight hours.

RESULTS

Culturing of spinal fluid on the three routine laboratory mediums alone resulted in an etiologic diagnosis in 41 of 51 cases, or 80 per cent. The chick embryo culture revealed the causative organism in 49 out of 51 cases, or 96 per cent. Of the group of cases of meningitis in which testing was done by culturing the spinal fluid on the chick embryo, the organism was a meningococcus in 36 cases, a pneumococcus in 6 and Hemophilus influenzae in 5, and in 1 each it was a beta hemolytic streptococcus and a hemolytic Staphylococcus aureus. In 2

cases of a disease clinically meningococcic meningitis and intensively treated as such, the cultured material failed to yield organisms either by the conventional or by the chick embryo method, and presumably was free of viable meningococci. In most cases growth on the egg was extremely rapid, and the smear revealed bacteria within six to eight hours. In only 2 instances was twenty-four hours required for growth, and once a culture became positive only after forty-eight hours. On the other hand, there was a frequent initial "lag" in growth on ordinary culture mediums which prevented 49 per cent of all cultures from being reported positive until two to three days after inoculation, while another 11 per cent required four or five days for growth. The growth of H. influenzae and pneumococci was particularly rapid on the chick embryo; hence early typing and prompt specific therapy could be undertaken.

In 5 cases during chemotherapy, one or two follow-up spinal fluid cultures made in the chick embryo were positive when comparative routine cultures already had become negative. This result tends to confirm earlier observations that the embryonic tissues are peculiarly suited to increase the viability of organisms weakened by chemotherapy.[5]

In 5 cases of meningococcemia with characteristic petechiae, lumbar puncture at the time of the patient's entry revealed clear spinal fluids with normal cell counts and with normal chemical composition. These spinal fluids were cultured both by the routine methods and on chick embryos. The inoculum into the eggs was made as large as was possible without touching the shell window; it varied between 1.5 and 2.5 cc. In 2 cases there proved to be viable meningococci in the spinal fluid by this method when routine cultures were negative. Undoubtedly, a frankly purulent meningitis was prevented by early chemotherapy of the meningococcemia.

In 4 cases of empyema due to hemolytic Staph. aureus, materials were cultured repeatedly by conventional methods and by the chick embryo technic. In 3 cases primary isolation of organisms was accomplished in the egg in less than eighteen hours, whereas conventional mediums required forty-eight hours. Under intensive treatment with sulfadiazine and penicillin the chick embryo culture proved to be the most rapid method for the demonstration of the poorly viable organisms (table 2).

It is of interest that after the diagnosis of "right lower lobe pneumonia with minimal effusion" was made, thoracentesis permitted withdrawal of only 0.5 cc. of clear thin fluid, which failed to yield organisms on smear and by routine culture but which on the chick embryo grew an abundant number of staphylococci. A diagnosis of "developing empyema" was therefore made by the egg culture of perfectly clear fluid in the earliest effusion stage of the lobar pneumonia.

II. IN VIVO STREPTOMYCIN SENSITIVITY TEST

The clinician is interested chiefly in determining in a short time whether a patient's pathogenic organisms will respond to therapeutic levels of an antibiotic substance. To this end various sensitivity tests have been introduced, based in general on the methods for the assay of the antibiotic substance.

The first practical method for the assaying of an antibiotic substance was furnished by Fleming [7] in 1929, with the utilization of serial dilutions. Rammelkamp [8] further developed this method and adapted it to clinical studies of antibiotic activity. Foster [9] described the highly accurate though complicated turbidimetric method, which has not been used widely for routine assays. According to Foster and Woodruff,[10] a modification of the Oxford cup method [11] has been of the greatest value and was practical from a clinical point of view, especially when a large number of assay determinations were made daily.

TABLE 2.—*Serial Cultures of Empyema Fluid Due to Hemolytic Staph. Aureus*

Patient R. O.: A 4 month old white boy with a diagnosis of pneumonia of the right lower lobe and effusion.

Hospital Day	Fluid Type	Smear	Blood Agar	Brain Broth	Chick Embryo Culture
2	Clear thin	Negative	No growth	No growth	Growth after 16 hours of incubation
6	Purulent	Negative	Growth after 48 hours	No growth, 48 hours	Growth after 4 hours
9	Purulent	Negative	No growth	No growth	Growth after 5 hours
15	Purulent	Negative	Growth after 48 hours	No growth, 48 hours	Growth after 5 hours
16	Purulent	Negative	No growth	No growth	Growth after 6 hours
25	Purulent	Negative	Growth after 72 hours	No growth, 72 hours	Growth after 6 hours

All clinically useful procedures for the determination of sensitivity to streptomycin now in use are "in vitro" methods. The true end point and clinical significance are difficult to interpret because the degree of susceptibility of an organism to an antibiotic substance as determined

7. Fleming, A.: On Antibacterial Action of Cultures of Penicillium, with Special Reference to Their Use in Isolation of B. Influenzae, Brit. J. Exper. Path. **10**:226, 1929.

8. Rammelkamp, C. H.: A Method for Determining the Concentration of Penicillin in Body Fluids and Exudates, Proc. Soc. Exper. Biol. & Med. **51**:95, 1942.

9. Foster, J. W.: Quantitative Estimation of Penicillin, J. Biol. Chem. **144**:285, 1942.

10. Foster, J. W., and Woodruff, H. B.: Microbiological Aspects of Penicillin: Methods of Assay, J. Bact. **46**:187, 1943.

11. Abraham, E. P.; Chain, E.; Fletcher, C. M.; Florey, H. W.; Gardner, A. D.; Heatley, H. G., and Jennings, M. A.: Further Observations on Penicillin, Lancet **2**:177, 1941.

by an "in vitro" test may vary greatly from the sensitivity of the same organism as judged by the clinical response of the patient.

The results obtained by the prolonged use of chick embryo cultures as a diagnostic aid suggested the employment of this technic in an "in vivo" test for streptomycin sensitivity. The chick embryo has been used in the study of chemotherapeutic agents by several investigators [12] and has proved a most susceptible living medium. The test to be described determines the amount of streptomycin necessary to inhibit growth of the organism in twenty-four hours on the chorioallantoic membrane of an 8 or 9 day old chick embryo.

METHOD

The streptomycin dilutions used were made up with sterile saline solution in rubber-stoppered bottles. The solutions ranged in strength from 1,000 units to 0.1 unit per cubic centimeter. The bottles were placed in the refrigerator when not in use. There is no appreciable deterioration of streptomycin over a period of several weeks. Fertile eggs in the eighth or ninth day of incubation were prepared for inoculation as described in the first part of this paper. Unless the approximate sensitivity of an organism is known, the test is best done in two parts. For the preliminary test on organisms of unknown susceptibility to streptomycin, we have arbitrarily used 100 units, 50 units, 15 units and 5 units per cubic centimeter for each chick embryo. One cubic centimeter of the streptomycin dilution selected was dropped into the space overlying the chorioallantoic membrane. Next, 0.1 to 0.2 cc. of a saline suspension of the organism to be tested was added. This suspension should contain between 10,000 and 100,000 organisms as determined by nephelometric standards. At twenty-four hours, smears were made from the surface of the chorioallantois and the presence of organisms determined with Gram's stain. We have always found the point to be sharp at this twenty-four hour period, and the smears usually were definitely positive at a concentration of streptomycin insufficient to prevent growth, while no organisms were found at levels of streptomycin sufficient to inhibit growth. When the approximate range of sensitivity was found at twenty-four hours, more exact determinations were made by setting up concentrations of streptomycin between the lowest level which inhibits growth at twenty-four hours and the highest level which permits growth to take place. These results are available twenty-four hours later. In the approximate determinations of streptomycin in body fluids which may be made parallel to the aforementioned sensitivity test, 1 cc. of the fluid to be tested is inoculated in the chick embryo instead of the known streptomycin dilution. The use of the patient's

12. Footnotes 3 and 4.

own organisms in this test is advised because of the known antigenic properties of most human serums against the standard strain of Escherichia coli used for determinations of streptomycin sensitivity.

RESULTS

In table 3 results are arranged to show the level of streptomycin necessary to inhibit growth as well as the next lower concentration used which allowed growth in twenty-four hours. Results are expressed in units of streptomycin per egg. The standard strain of E. coli (Waksman) required 5 units per chick embryo for inhibition but was always sensitive to 1 unit per cubic centimeter by the in vitro method. This

TABLE 3.—*Streptomycin Sensitivity of Representative Organisms*

Organism	Units of Streptomycin Which Will Inhibit Growth, Units/Egg	Units of Streptomycin Which Will Permit Growth, Units/Egg	Calculated 5 to 1 Ratio for Comparison with In Vitro Tests *	
			Units for Inhibition	Units for Growth
Aerobacter aerogenes (resistant strain)	>1,000	>1,000	>200	>200
Aerobacter aerogenes (sensitive strain)	2	1	0.4	0.2
Corynebacterium diphtheriae	30	22.5	6	4.5
Eberthella typhi	100	75	20	15
Escherichia coli (Waksman strain)	5	4	1	0.8
Escherichia coli	5	4	1	0.8
Hemophilus pertussis	6	3	1.2	0.6
Neisseria gonorrhoeae	5	2	1	0.4
Pseudomonas aeruginosa	50	15	10	3
Salmonella aertrycke	100	75	20	15
Vibrio comma	100	75	20	15
Virus of psittacosis	>500	>500	>100	>100
Virus of lymphogranuloma venereum	>500	>500	>100	>100

* One unit of streptomycin, an S unit, is defined as that amount of material which when present in 1 cc. of nutrient medium will just inhibit the growth of a standard strain of E. coli.

5 to 1 ratio is listed in adjacent columns for other organisms, so that comparison may be made with expressions of unitage generally employed (table 3).

Comparison of the values obtained by streptomycin sensitivity tests performed by different methods and in different laboratories reveals rather wide discrepancies. These are present even when identical strains of certain standard organisms are used, and undoubtedly this is due to the great number of variants encountered in each test. In most cases the values obtained are significant only in comparison with others similarly obtained, so that each laboratory has to determine its own standards. Perhaps the most important variant of the "in vitro" tests is the chemical composition of the agar or broth used. Significant changes in the apparent sensitivity to streptomycin of certain organisms are encountered with changes in p_H and in the presence and concen-

tration of phosphates, dextrose, cysteine and salts.[13] All these factors are relatively constant in the chick embryo of a given age, and this medium is also ready-made and sterile and needs no other standardization. Another advantage lies in the wide range of streptomycin concentrations which may be investigated. The chick embryo method has also been used by us in the determination of sensitivity to penicillin, and the results clinically have been satisfactory.

SUMMARY AND CONCLUSIONS

The results of this study of 51 cases of meningitis are in agreement with those of Blattner, Heys and Hartmann, and they show that the chick-embryo culture technic affords a rapid and accurate method for the demonstration of pathogens in bacterial meningitis. The bacteriologic diagnosis was made in 96 per cent of all cases in which this method was used, as compared with 80 per cent of those in which the conventional methods were employed.

The rapidity of the etiologic diagnosis was increased many fold. This permitted the institution of specific therapy in a few hours, as compared with the several days which frequently must elapse when conventional methods of culture are used.

By using chick embryo cultures it is possible to demonstrate the presence of organisms in spinal fluid when the latter shows no alteration in its cytologic or chemical nature.

An in vivo streptomycin sensitivity test employing the chick embryo has been devised, and the streptomycin sensitivity of a number of organisms has been determined.

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13. Waksman, S. A.; Bugie, E., and Schatz, A.: Isolation of Antibiotic Substances from Soil Microorganisms, with Special Reference to Streptothricin and Streptomycin, Proc. Staff Meet., Mayo Clin. **19**:537, 1944. Geiger, W. B.; Green, S. R., and Waksman, S. A.: The Inactivation of Streptomycin and Its Practical Applications, Proc. Soc. Exper. Biol. & Med. **61**:187, 1946. Denkelwater, R.; Cook, M., and Tishler, M.: The Effect of Cysteine on Streptomycin and Streptothricin, Science **102**:12, 1945.

ADENOMAS OF THE LARGE INTESTINE IN CHILDREN

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THERE are few comprehensive studies recorded in the literature regarding the incidence of adenomas of the large intestine in children and in young people. Estimations of the incidence of adenomas vary with the type of material used for investigation. Thus different results are obtained if the adenomas are noted as a result of clinical symptoms directing attention to the large intestine than if they are noted in the large intestine at autopsy or in segments of the large intestine surgically resected. It is unlikely that many adenomas without accompanying manifest symptoms would be noted in young patients because few routine roentgenologic and proctoscopic examinations are done on this age group. If the material studied is obtained from autopsies or from surgical specimens, the incidence depends to a large extent on how carefully the specimen is examined. Small adenomas are easily overlooked when partially obscured by a mucosal fold.

Many authors use the term polyp to designate all sessile or pedunculated benign tumors arising from the mucosa. As a result of this interpretation, it is seldom clear whether the author is actually referring to adenoma, to some other type of benign tumor, such as lipoma, fibroma or leiomyoma, or even to an overgrowth of inflammatory tissue. The term polyp does not indicate the true nature of a tumor, and reviews of reports of polyps do not yield informative data unless the specific histologic type is given.

The present report is based on a study of 449 consecutive autopsies on persons under 21 years of age in which the entire large intestine was available for study. Each intestine was examined in the fresh state. All abnormal mucosal elevations together with the contiguous intestinal wall were removed and fixed in a 4 per cent solution of formaldehyde. The site and appearance of each lesion were noted and recorded. Serial and step paraffin sections through the lesion at a right angle to the intestinal wall were prepared and stained with hematoxylin and eosin. The microscopic structure was then noted and compared with the gross observations.

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In the present study, as noted in the table, no adenomas were encountered in patients in the first year of life. There were 3 patients with adenomas in the first decade. The youngest patient was a white boy, 4 years old, who died after rupture of an aneurysm of the basilar artery. An adenoma was situated in the rectum and measured 8 by 4 by 4 mm. The surface was smooth and gray, and the consistency was firm. There was a short stalk. The second patient was a white girl, aged 7 years, who died of tularemia. There was a single adenoma in the ascending colon, which measured 4 by 3.5 by 2.5 mm. The surface was smooth and dark red, and the consistency was soft. The normal mucosa appeared pulled up toward the adenoma, which was connected with the intestnial wall by a short stalk. The third patient was a Negro boy, aged 9 years, who died after an operation for removal of a pinealoma. There were 2 adenomas, measuring 4 by 3.5 by 3 mm. and 6 by 7 by 4 mm., respectively, located in the rectum. The external

Incidence of Adenomas

Age Groups, Years	Male Patients	Male Patients with Adenomas	Per Cent	Female Patients	Female Patients with Adenomas	Per Cent	Total Patients	Patients with Adenomas	Total Per Cent
0 to 1	161	0	0	123	0	0	284	0	0
1 to 10	56	3	5.3	29	0	0	85	3	3.5
11 to 20	49	0	0	31	2	6.4	80	2	2.5

surface of each adenoma was gray and finely lobulated, and the consistency was soft. Each tumor was attached to the intestinal wall by a pedicle 5 mm. long.

Among the patients in the second decade of life there were 2 with adenomas. The first was a Negro girl, 12 years old, who died of bronchiectasis and a pulmonary abscess. There was a single adenoma, 6 by 3 by 2.5 mm., in the rectum. The surface was soft, gray and smooth. There was a thin, narrow stalk 3 mm. in length. The second patient was a white girl, 15 years old, who died after a traumatic rupture of the liver and spleen. There was a soft, lobulated, sessile, gray adenoma in the cecum, measuring 10 by 5 by 3.5 mm.

The histologic structure of all of the adenomas was essentially similar (fig. 1, *A* and *B*). In some instances the adenomas appeared to arise on the tip of a mucosal fold. There was a central core of connective tissue, which in some specimens was short and attenuated and in others broad and irregular. Extending from the central core were finer branches of connective tissue which supported irregular glands. The glands were lined by columnar epithelial cells, with a general basal arrangement of the nuclei and a well defined basement membrane. Some of the glands were distended with mucus. The glands, especially in

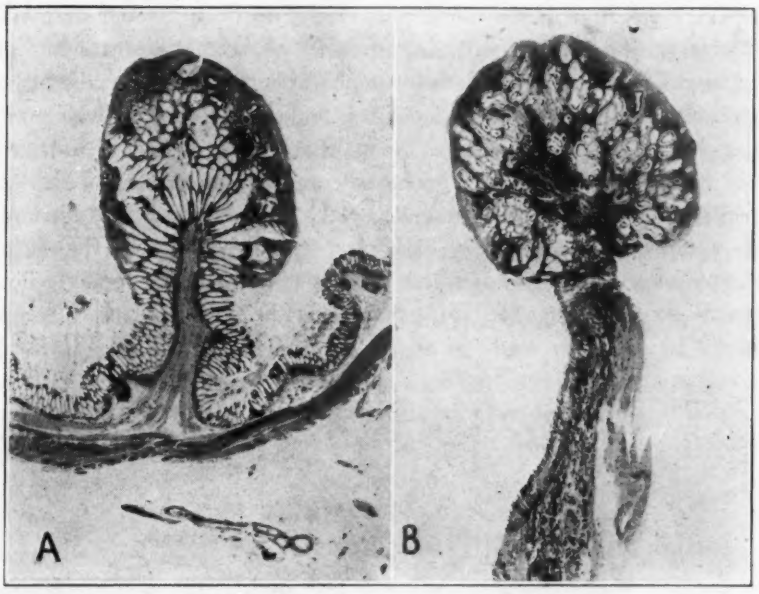

Fig. 1.—*A*, photomicrograph of an adenoma in the rectum of a 4 year old white boy. The adenoma appears to have arisen on a mucosal fold. The wall of the rectum is normal. × 4.5. *B*, photomicrograph of the larger of 2 adenomas in the rectum of a 9 year old Negro. As in 1 *A* there is a large amount of fibrous stroma in the periphery. × 4.5.

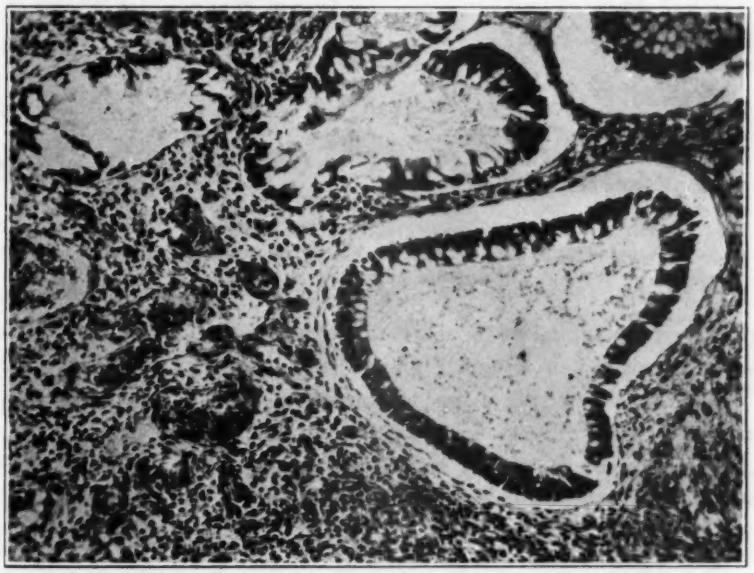

Fig. 2.—High power photomicrograph of the periphery of adenoma in figure 1 *B*. The stroma is infiltrated with inflammatory cells. The capillaries are hyperemic. × 130.

the peripheral zone of the adenomas, tended to be separated by a relatively large amount of stroma composed of connective tissue. The stroma was frequently heavily infiltrated with inflammatory cells, including plasma cells, lymphocytes and a few leukocytes, some of which were eosinophilic (fig. 2). In some areas the small capillaries and veins were dilated and hyperemic. There were occasional foci of red cell extravasation. Although segments of the periphery of the adenomas were composed of a papillary glandular structure, much of the surface consisted of a single layer of columnar epithelium covering richly cellular connective tissue (fig. 3). In a few fields the epithelium was desquamated. In a similar study of adenomas occurring in adults, including

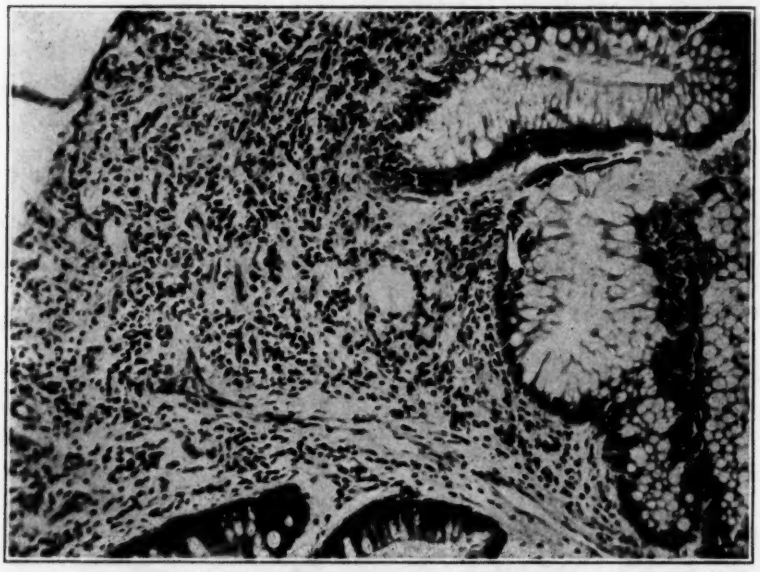

Fig. 3.—High power photomicrograph of the periphery of the adenoma in figure 1 *A*. A single layer of epithelial cells has partly desquamated from the surface. The stroma is infiltrated with inflammatory cells. × 130.

1 patient with familial adenomatosis, the periphery of the adenomas was usually comprised of irregular glands supported by a relatively scanty and delicate connective tissue framework.[1] Only occasionally were peripheral areas of adenomas in adults encountered in which the amount of connective tissue present exceeded the amount of glandular tissue. Diamond[2] noted in his case that the glands were embedded in an

1. Helwig, E. B.: The Evolution of Adenomas of the Large Intestine and Their Relation to Carcinoma, to be published.

2. Diamond, M.: Adenoma of the Rectum in Children, Am. J. Dis. Child. **57**:360-367 (Feb.) 1939.

edematous stroma and that there was an infiltration of inflammatory cells and areas of granulation tissue. David [3] stated that the common structure of adenomas in childhood was that of a mixed inflammatory and myxoid stroma containing small acinar cysts. It is probable that the fibrosis occurring in the adenomas in both young and old age groups is the result of inflammation in the tumor. However, it would appear that this change is much more conspicuous in adenomas in children.

Erdmann and Morris [4] classified adenomas into the adult (acquired) type and the adolescent (congenital, disseminated) type by reason of the clinical features. McKenney [5] has reported the occurrence of adenomas with multiple polyposis in 4 children of the same family, aged 2, 5, 9 and 11 years. He believed these tumors to be congenital in origin. Diamond also concluded that the adenomas in his case were congenital. In the present study there was no way of telling whether the adenomas were congenital. As previously mentioned, the histologic appearance of adenomas in children differed only in the amount of connective tissue stroma from those encountered in a much older group. Because adenomas occurring in children and in adults have a similar structure otherwise, it seems logical to conclude that the tumors are morphologically similar.

All of the adenomas in this series were incidental, and as far as is known they did not produce symptoms. Diamond [2] reported the occurrence of 2 adenomas, which produced constipation, in the rectum of a girl 30 months of age. One of the 2 adenomas in his case measured 2.5 cm. in diameter, and the other, 5 mm. in diameter. He collected reports of 24 apparently similar cases from the literature and stated that rectal adenomas are uncommon in children. Pennington [6] cited Bokay as having noted 25 instances of adenoma of the rectum among 58,970 children. Lawrence,[7] considering adenomas of the colon exclusive of the rectum, reported 5 in 166 patients in the first and second decades. In the present study no adenomas were noted in the large intestine in the first year of life, but in the remainder of the first decade there was an incidence of 3.5 per cent and in the second decade, an inci-

3. David, V. C.: Some Etiologic and Pathologic Factors in Cancer of the Large Bowel, Arch. Surg. **41**:257-286 (Aug.) 1940.

4. Erdmann, J. F., and Morris, J. H.: Polyposis of the Colon, Surg., Gynec. & Obst. **40**:460-468 (April) 1925.

5. McKenney, D. C.: Multiple Polyposis: Congenital, Hered-familial Malignant, Am. J. Surg. **46**:204-216 (Oct.) 1939.

6. Pennington, J. R.: A Treatise on the Diseases and Injuries of the Rectum, Anus and Pelvic Colon, Philadelphia, P. Blakiston's Son & Co., 1923, p. 484.

7. Lawrence, J. C.: Gastrointestinal Polyps: Statistical Study of Malignancy Incidence, Am. J. Surg. **31**:499-505 (March) 1936.

dence of 2.5 per cent. On the basis of these observations adenomas of the large intestine are uncommon but not rare in children.

Kennedy [8] reported on the occurrence of polyps of the rectum and colon in 49 infants and children. He included both benign and malignant tumors in his study, but he lacked reports of histologic examinations on many of the tumors because they were removed by fulguration. Nearly half of his patients were between 4 and 6 years of age. Diamond noted that 9 of 12 patients with adenomas of the rectum whose cases were recorded in the literature were between 2½ and 10 years of age. David [3] also stated that adenoma of the rectum is usually observed in children from 3 to 10 years old. In the present study, which includes the entire large intestine, the patients were 4, 7, 9, 12 and 15 years of age. It would appear from the present study and from reports in the literature that adenomas of the colon and rectum are decidedly uncommon in the first two years of life.

Among the 449 large intestines examined for the present report, no benign tumors other than adenomas were observed. This is in contrast to the observations I have made on an older group of patients.[9] In the patients above 30 years of age lipoma, leiomyoma and carcinoid were noted. Judging from these observations, benign tumors other than adenoma appear to be rare in childhood.

None of the adenomas in the present series showed gross or microscopic evidence of malignant change. In a few adenomas a part of the glandular structure was obliterated by an inflammatory process and by proliferation of connective tissue. Sometimes only a few isolated epithelial cells were present. It is conceivable that the picture in such a field might be mistaken for invasion in the absence of the remainder of the adenoma.

Although some investigators believe that adenomas of the large intestine arise on the basis of an antecedent diffuse inflammation, the intestines in the present study did not show evidence of a previous inflammation. The observations made in this study agree with the concept that adenomas of the large intestine are true tumors and not the result of a diffuse inflammatory process.

SUMMARY

Adenomas of the large intestine are uncommon but not rare in children. Exclusive of the first year of life, approximately 3 per cent of children have adenomas.

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8. Kennedy, R. L. J.: Polyps of the Rectum and Colon in Infants and in Children, Am. J. Dis. Child. **62**:481-488 (Sept.) 1941.

9. Helwig, E. B.: Benign Tumors of the Large Intestine—Incidence and Distribution, Surg., Gynec. & Obst. **76**:419-426 (April) 1943.

Only those adenomas of sufficient size to produce symptoms are likely to be noted in clinical investigations because of the difficulty in doing proctoscopic and roentgen examinations on children.

Isolated adenomas of the large intestine in childhood commonly show foci in which the glandular structures are embedded in a stroma of cellular connective tissue infiltrated with inflammatory cells.

Benign tumors of the large intestine other than adenomas are rare in children.

BRONCHIECTASIS FOLLOWING PRIMARY TUBERCULOSIS

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MANY infections of childhood have been assigned etiologic responsibility in bronchiectasis. In recent years a few communications have indicated that pathogenic factors often seem to occur during the course of primary tuberculosis and might quite conceivably produce ectasia. In 1933 Jones and Cournand [1] discussed the shrunken lobe with bronchiectasis. They carefully described the pathogenic factors involved, mentioning enlarged lymph nodes in primary tuberculosis as being possible factors, particularly in involvement of the middle lobe. Brock and his co-workers [2] suggested (1937) that obstructive lesions giving rise to the roentgenologic picture of so-called epituberculosis might eventuate in bronchiectasis. They illustrated this contention with a case history. In 1942 Kent [3] provided further evidence by demonstrating residual asymptomatic bronchiectasis in 7 of 10 children who had previously shown roentgenographic evidence of pulmonary atelectasis during the course of primary tuberculosis.

In 1942 a study from the Maybury Sanatorium gave data [4] which related tuberculosis of the bronchi to atelectasis, or obstructive pneumonitis. It revealed that the roentgenograms of 12 per cent of 716 children admitted over a five year period showed a dense, more or less homogeneous and usually segmental or lobar shadow (that suggested obstructive pneumonitis). Forty-two of the patients with this syndrome

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From the William H. Maybury Sanatorium (Detroit Municipal Tuberculosis Sanatorium).

1. Jones, O. R., and Cournand, A.: Shrunken Pulmonary Lobe with Chronic Bronchiectasis, Am. Rev. Tuberc. **28**:293 (Sept.) 1933.

2. Brock, R. C.; Cann, R. J., and Dickinson, J. R.: Tuberculous Mediastinal Lymphadenitis in Childhood: Secondary Effects on the Lungs, Guy's Hosp. Rep. **87**:295 (July) 1937.

3. Kent, E. M.: Bronchial Obstruction and Pulmonary Atelectasis as Seen in Childhood Tuberculosis with Secondary Bronchiectasis as Sequela, Am. Rev. Tuberc. **46**:542 (Nov.) 1942.

4. Jones, E. M.; Rofferty, T. N., and Willis, H. S.: Primary Tuberculosis Complicated by Bronchial Tuberculosis with Atelectasis (Epituberculosis), Am. Rev. Tuberc. **46**:392 (Oct.) 1942.

were examined bronchoscopically, and 31 of them were found to have tuberculous involvement of a bronchus, which was present as ulceration, granulation tissue or tuberculoma or as extrinsic pressure from enlarged tuberculous lymph nodes. Such lesions appeared to interfere with normal bronchial cleansing. In the course of this study it was observed by the examination of bronchograms that certain of these children (e. g. the patient in case 4 of that study) had bronchiectasis in the region of the obstructive pneumonitis.

Several years after this demonstration a number of these children were recalled, together with other children having the same phenomenon but more recently admitted. They were brought back for evaluation of their present condition and especially for a survey of their bronchial system by bronchography. Altogether the bronchi of 37 children have been surveyed in this manner (table 1).

TECHNIC

Anesthesia of the pharynx and of the tracheobronchial tree is quite necessary for accurate mapping of a lobe or lung. In spite of the advan-

TABLE 1.—*Bronchograms of Children Who Formerly Had Obstructive Pneumonitis*

Children	No.
Previously showing obstructive pneumonitis, returned for bronchogram	37
With satisfactory bronchogram	34
With inadequate filling of former diseased area	3
Showing bronchiectasis in area of former pneumonitis	24
Showing no bronchiectasis	10

tages of anesthesia, however, mapping of the lung in children as young as 5 years is fraught with difficulties, not the least of which is the behavior of the child during the procedure. The children in this study had all been patients in the sanatorium previously, and they felt secure. They knew that others of their age (which ranged from 5 to 16 years) were undergoing the same test and therefore took considerable responsibility for and pride in a successful result. They were told what was planned and were cautioned emphatically against swallowing, coughing or stalling for time during the anesthetizing and the placing of the catheter and until the roentgenogram was taken.

Food was withheld for at least eight hours before the instrumentation, and no water was allowed for four hours prior to it except that needed with the oral medication. On the morning of the test, the teeth were brushed as usual and a 25 per cent solution of alcohol was used as a mouth wash and gargle. For an hour or longer before the test, they lay in the position most favorable for draining possible mucus or secretion from the area of previous pulmonary disease. Thirty minutes before

the anesthesia they were given, by mouth, codeine, atropine and pentobarbital sodium in doses sufficient to depress the cough, dry the mouth and have a sedative effect. The doses varied obviously in respect to age.

After this, one puff of an atomizer sprayed a 3 per cent solution of cocaine hydrochloride into the pharynx, and the patient was observed for evidence of sensitivity to this drug, especially for tachycardia. Then anesthesia of the pharynx was completed by spraying, and approximately 1 to 2 cc. of a 3 per cent solution of cocaine hydrochloride was dropped into the trachea while the patient was in the upright position. About the same amount was added drop by drop into the trachea while the patient leaned toward the side to be mapped. No child received less than 1 cc.; some were given as much as 3 cc. The relative smallness of the pharynx and the largeness of the tonsils required complete insensitivity to the touch of the mirror. Per pound of body weight the children probably received more cocaine than the average adult does in going through the procedure. Untoward effects were watched for carefully. A precalculated dose of a rapidly acting barbiturate for intravenous or intramuscular use was in readiness, but in no instance was it needed. Even with the use of atropine many of the children drooled considerably.

Unler a laryngeal mirror a no. 14 catheter held in the required shape by a no. 12 wire was introduced into the larynx. The wire was then withdrawn and the catheter advanced toward the carina. Under fluoroscopic control, the catheter was advanced into the proper main bronchus. This was facilitated by turning the patient's face toward the opposite side and rotating the catheter slightly.

Five to 10 cc. of iodized poppyseed oil 40 per cent at room temperature was used. The proper lobe was filled by placing the child in the most advantageous position, taking care to fill all the bronchi of each segment and particularly to avoid filling the alveoli.

Posterior-anterior and lateral roentgenograms were made in all cases, and in some, stereoscopic and oblique films. Not more than one lung was mapped at one sitting.

After satisfactory roentgenograms had been made the patient was kept for several hours in the optimal position or positions for elimination of the iodized oil (with head down and the proper side elevated). The child was instructed to clear his throat and to avoid hard coughing. In some cases practically no oil was seen on fluoroscopic examination the next day, and few had evidence two weeks later. Rapid and complete elimination is possible if the oil does not get into the alveoli.

About four hours after the anesthesia was started, the patients were given a saline cathartic with plenty of water to eliminate the swallowed iodized oil. An hour after this they were allowed to eat. No definite reactions or after-effects developed which could be attributed to either the cocaine or the iodized oil.

ANALYSIS OF RESULTS

The children varied in age from 2 to 12 and had a mean age of 5½ years. The duration of the obstructive lesions could be followed from admission to clearing, and usually the time of onset could be placed rather accurately by symptoms. The duration of the obstructive lesion appeared to have some relation to the establishment of bronchiectasis, because only 1 child in the group without ectasis (1 in 10) had had his disease as long as nineteen months, while 10 out of 24 with ectasis had evidence of disease from nineteen to thirty months.

Table 2 indicates some of the time relationship and shows that by far the larger number of children in whom bronchiectasis developed had had the pulmonary lesion longer than one year. In fact, only 4 of the 24 in whom bronchiectasis was manifest had had their lesion twelve months or less, but 20 of the 24 having ectasis had been ill thirteen months or longer. While the children who had no bronchiectasis are

TABLE 2.—*Relation Between Duration of the Lesion and the Presence of Bronchiectasis*

Duration of Disease, Onset to Clearing, Mo.	Bronchiectasis				Total	
	Present, Cases		Not Present, Cases			
	No.	Per Cent	No.	Per Cent	No.	Per Cent
1 to 12	4	11.8	5	14.7	9	26.5
13 and over	20	58.8	5	14.7	25	73.5
Total	24	70.6	10	29.4	34	100.0

equally divided, only 1 in the group had the disease as long as nineteen months. Iodized poppyseed oil was instilled at a mean interval of three and one-half years after roentgenologic clearing. This indicated that the damage to the bronchi was permanent.

Analysis of the results as presented in table 1 shows that instillation of radiopaque material occurred at the site of former disease in 34 of the 37 children. Of the 34, unquestioned bronchiectasis was present in 24, or 70 per cent (table 1). The lesion was distributed equally between the two lungs, with 12 children showing ectasis on the right and 12 on the left. There was a preference for localization in the anterolateral branch of the upper lobe bronchus and in the apical branch of the lower lobe bronchus (see table 3). No ectasis was discovered in the lingula. This is of interest because bronchiectasis in tuberculous adults has been found quite commonly in this part of the lung.[5] Several typical case histories illustrate significant features of the work and are reported.

5. Jones, E. M.; Peck, W. M., and Willis, H. S.: Bronchiectasis Following Tuberculosis in Adults, to be published.

The roentgenographic pattern was often complex, depending on the fluctuation of the associated bronchial disease. In those cases in which the lesions were viewed in the inception they characteristically showed the parenchymal infiltration and the enlarged lymph nodes of the primary complex, but with the appearance of bronchial obstruction a homogeneous opacity, notable for its strict segmental arrangement, developed tributary to the bronchial lesion and usually in the neighborhood of the primary focus. This parenchymal opacity might then extend or recede in a manner corresponding to the varying completeness of the obstruction and to the amount of secretion elaborated by the parenchymal lesion. At times it appeared that the bronchial lesion or its associated edema might be so extensive as to obstruct bronchi to neighboring segments or lobes devoid of primary infection (as shown in case 2), causing some of the latter to collapse with classic, reversible atelectasis. This secondary involvement might also fluctuate, at times producing a

TABLE 3.—*Distribution of Bronchiectasis by Lobe and Segment*

Lobe		Segment					
Right Side	Left Side	Apical	Antero-lateral	Postero-lateral	Antero-basal	Medial Basal	Total No.
Upper	.....	..	3	1	..	..	4
Middle	.....	..	..	..	..	..	4
Lower	.....	1	..	..	1	2	4
	Upper	1	6	2	..	..	9
	Lingual	..	..	..	..	..	0
	Lower	3	..	..	..	..	3
Cases of bronchiectasis, total							24
Cases without bronchiectasis							10
Total cases with injection of iodized poppyseed oil							34

bewildering picture of atelectasis migrating or moving unexpectedly from one related segment to another. These obstructive phenomena are the more understandable when one considers the small size of the young child's bronchus and its capacity to undergo anatomic and physiologic obstruction from relatively scant secretion, inflammation, edema or extrinsic pressure. Clearing of these areas of true atelectasis seemed to be complete without residual damage. On the other hand, clearing of the pneumonitis in the segments or lobes harboring the primary focus often left fibrosis and bronchiectasis in its wake. The severity of the process obviously could not be estimated by the roentgenogram alone. The duration and the degree of obstruction, the extent of the original primary disease and the amount of drainage therefrom appeared to be the factors vital in influencing the residual bronchial damage.

REPORT OF CASES

CASE 1.—Tuberculosis in this 9 year old Negro boy, J. E., was found during a neighborhood roentgenologic survey. On admission to the sanatorium he

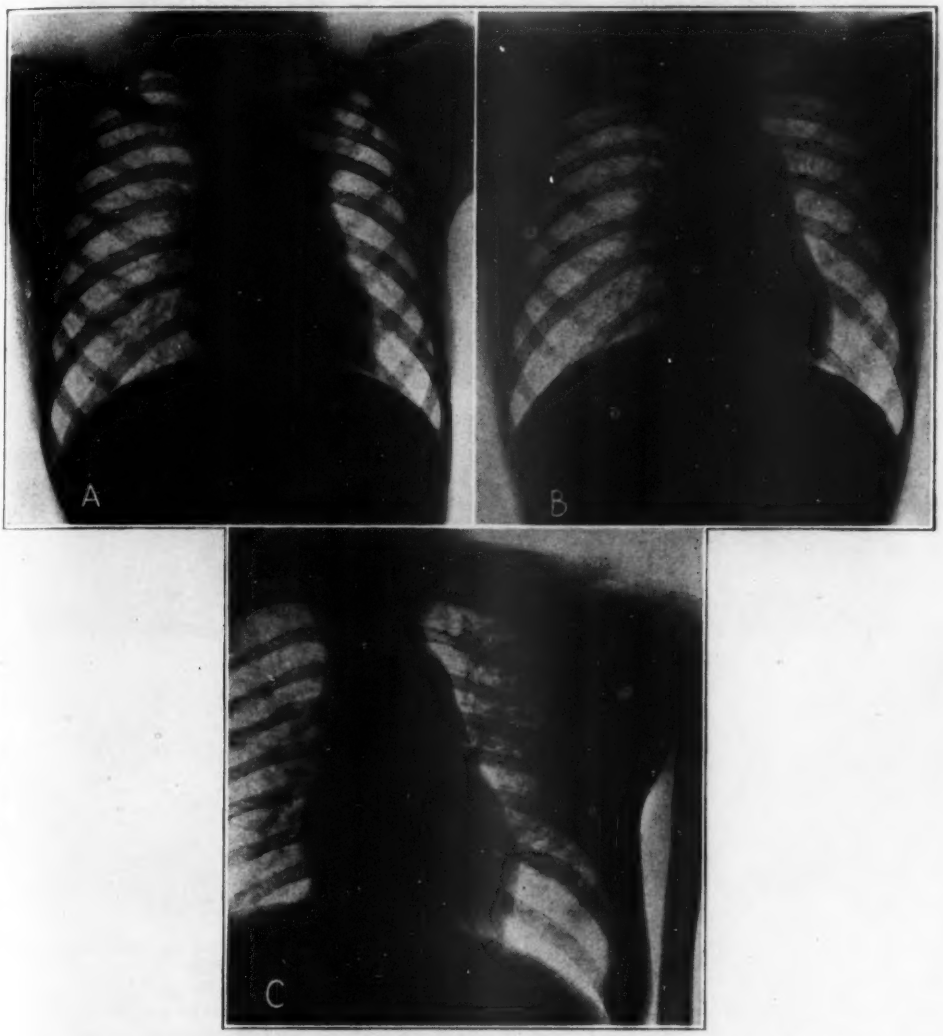

Fig. 1 (case 1).—*A*, a roentgenogram showing an exudative lesion in the upper part of the left lung, with an area suggestive of a cavity. A neighborhood survey discovered this 9 year old boy's tuberculosis on Sept. 9, 1943, and he was admitted to the sanatorium the same month. Gastric cultures were positive for more than eighteen months. He had practically no symptoms, and the results of bronchoscopy were negative. *B*, a roentgenogram taken June 12, 1945, twenty-one months after that shown in figure *A*. Gradually the lesion cleared and calcium appeared in the lymph nodes. Residual pulmonary fibrosis and calcium in lymph nodes at the root are obvious. *C*, a bronchogram, taken Aug. 6, 1945, twenty-three months after admission and two months after figure *B*, showing bronchiectasis in the apical branch of the upper lobe of the left lung. The bronchi are involved from the root to the periphery. The general condition is excellent, and there are no symptoms or signs of bronchiectasis.

appeared chronically ill and tired, but he had practically no cough or anorexia. Breath sounds and resonance were decreased over the upper part of the left lung. A few rales were heard on two occasions, a year apart. Cultures of sputum revealed tubercle bacilli at the time of the patient's admission, and gastric

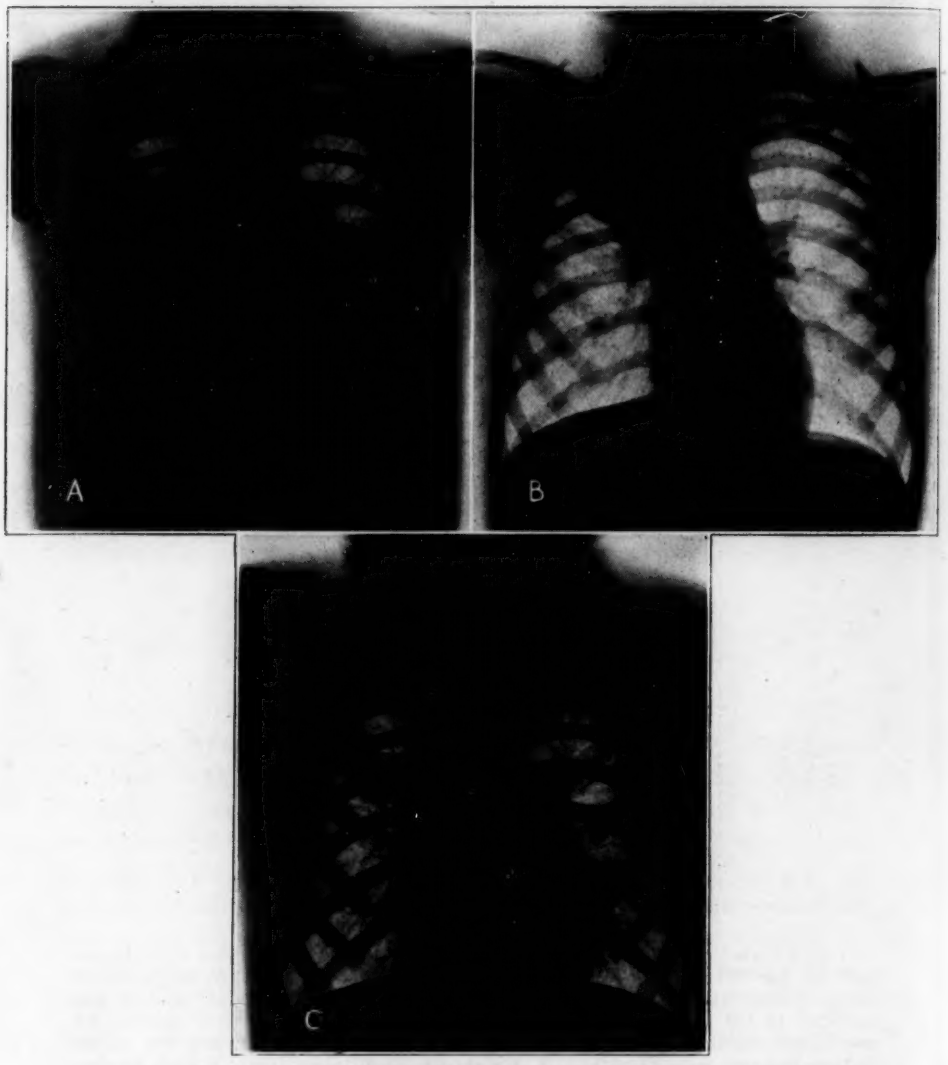

Fig. 2 (case 2).—*A*, a roentgenogram taken at the time of the patient's admission (May 8, 1942), showing extensive enlargement of the lymph nodes at and above the root on the right and extensive infiltration into the anterolateral segment of the upper lobe of the right lung. *B*, a bronchogram showing extension of "opacity" to involve the entire upper lobe (Jan. 7, 1943). Bronchoscopic examination revealed bulging and secretions in the bronchus of the upper lobe. *C*, a roentgenogram made one year after figure *B* (Jan. 25, 1944). Gross lesions have cleared, leaving residual fibrosis in the anterolateral segment.

materials, cultured repeatedly, contained the organisms for eighteen months, the last positive culture being seven months before the bronchogram was made. Bronchoscopic examination three weeks after admission revealed nothing abnormal —not even secretions. Gradually the lesion healed, leaving some fibrosis in the parenchyma and calcium in the lymph nodes. The general condition was excellent most of the time, and no symptoms of bronchiectasis appeared. The bronchogram, however, showed extensive bronchiectasis, as illustrated in figure 1 *A*, *B* and *C*.

CASE 2.—Following eight months of contact with tuberculosis, tuberculous conjunctivitis and a "cold" with slight cough developed in this 6½ year old Negro boy (J. W.). A roentgenogram taken at that time (figure 2 *A*) showed primary tuberculosis in the anterolateral segment of the upper lobe of the right lung and an extensive enlargement of lymph nodes at the root of that lung. Cultures of sputum, gastric contents and stool failed to reveal tubercle bacilli at the time of the patient's admission. Impairment of resonance and suppression of breath sounds

Fig. 3 (case 2).—*A*, a bronchogram (Jan. 28, 1944) made three days after figure *B*, showing cylindric bronchiectasis in the anterolateral segment of the upper lobe of the right lung—the seat of the primary focus. *B*, a lateral roentgenogram (Jan. 28, 1944) showing that the dilatation extends from root to periphery.

were present, but there were no rales and no wheezes. Three months after admission a slight wheeze developed on the right side. The rectal temperature rose to 101 F. on one day and again for one day three weeks later. At this time the lesion shown in the roentgenogram had increased moderately, and the cultures became positive. Bronchoscopic examination revealed a considerable amount of mucopurulent secretion and bulging of the wall of the right main bronchus. Figure 2 *B* represents the height of the lesion, now involving the upper lobe. Bronchoscopic examinations were made periodically and showed decrease in secretion and diminution in the size of the bulge over a six month period. Eight months after the first bronchoscopic examination, the bulging had disappeared and the secretions were greatly reduced.

Cultures ceased to yield tubercle bacilli fifteen months after the first bronchoscopic examination and two and a half months before the bronchogram was made. The roentgenogram (fig. 2 *C*) showed fibrosis in the anterolateral segment of the upper lobe of the right lung, and the bronchogram showed (fig. 3 *A* and *B*) bronchiectasis involving these bronchi from the root to the periphery. There were no symptoms or signs of bronchiectasis except in the bronchogram.

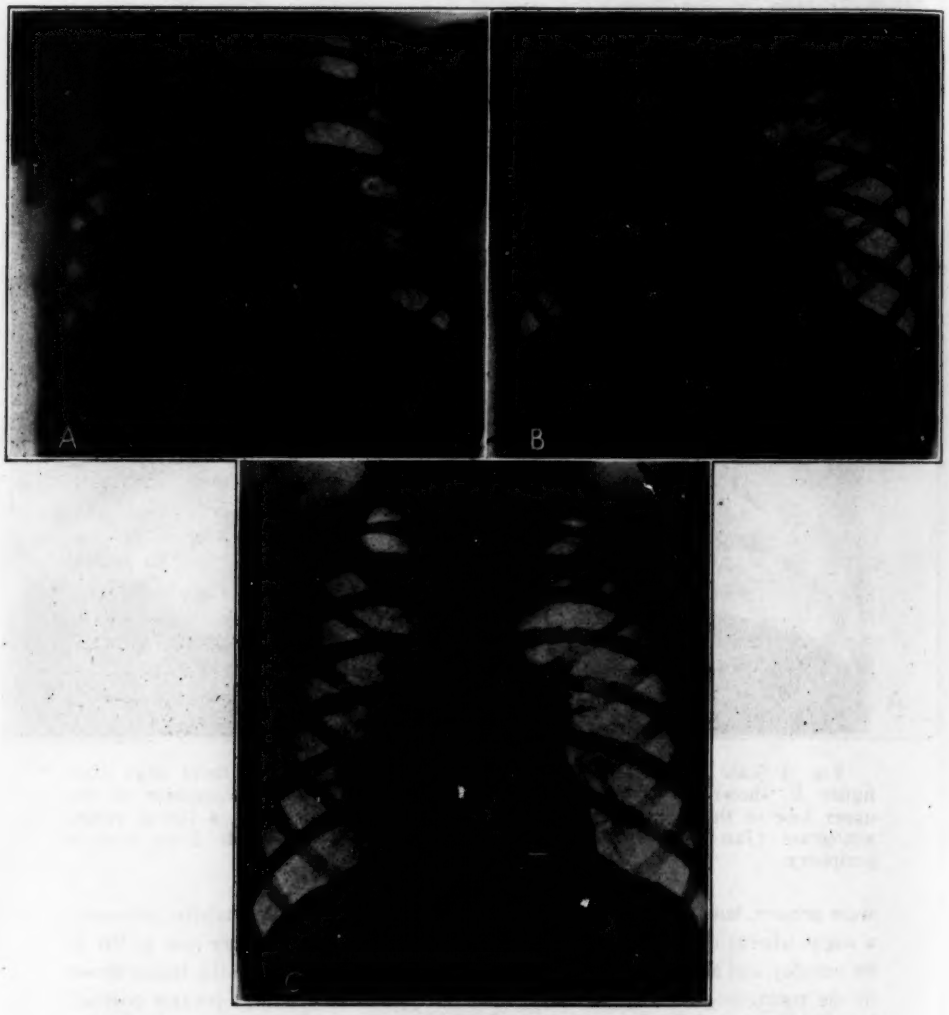

Fig. 4 (case 3).—*A*, a roentgenogram made at the time of the patient's admission (May 17, 1941) showing a large area of dense consolidation in the middle lobe and the anterolateral segment of the upper lobe of the right lung. A lateral roentgenogram at that time showed enlargement of lymph nodes at the root. *B*, a roentgenogram (Nov. 15, 1941) made at the highest development of the fever, cough and the lesion, which includes the cavity. *C*, residual fibrosis (Aug. 3, 1943) approximately two years after the patient's admission.

CASE 3.—L. J., a 5½ year old Negro girl, had known contact with tuberculosis before a cough, high fever, dyspnea and fatigue developed. Three weeks after the onset of the symptoms, a roentgenogram showed consolidation in the lower part of the right lung. At this time she was under treatment in a general hospital for pneumonia. Reaction to the tuberculin test was strongly positive. She was transferred to the sanatorium on May 16, 1941 (fig. 4 *A*), after about two months of illness. She was well nourished and in no distress but weak and had a rapid pulse. There were impaired resonance and decreased breath sounds over the lower half of the chest anteriorly but no rales; wheezing was pronounced. Tubercle bacilli were found on culture of the gastric contents. She had a continuous low grade fever, with bouts in which the temperature rose to 103.2 F. The consolidation gradually increased in size. Bronchoscopic examination on Sept. 4, 1941 showed a tuberculoma on the anteromedial wall in the region of the middle lobe

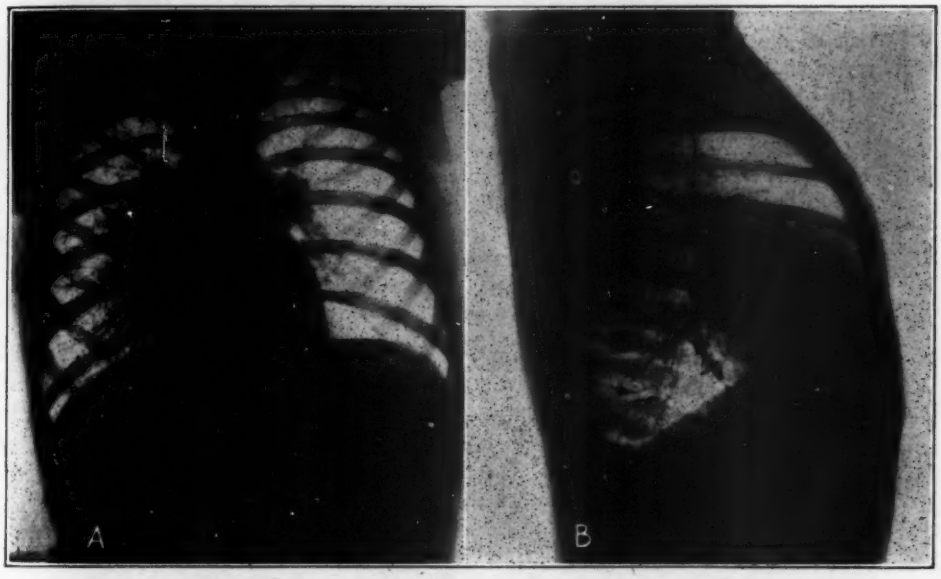

Fig. 5 (case 3).—*A*, a bronchogram (Aug. 18, 1943) showing bronchiectasis in the middle lobe and the anterolateral segment of the upper lobe of the right lung (fig. 4 *A* and *B*). *B*, a lateral roentgenogram showing the degree and type of bronchiectasis.

bronchus. Sectioning of the partially removed tissue revealed tubercles. On repeated bronchoscopic examinations from October 1941 through May 1942, there were thick, heavy secretions and a perforation of the bronchial wall through which cheesy lymph node material was entering the bronchial lumen. In August 1942, there was no ulceration but considerable tenacious, mucopurulent sputum. At the last examination, Dec. 17, 1942, a moderate amount of secretion was still present. The total white blood cell count varied from 11,500 per cubic millimeter with 78 per cent polymorphonuclear leukocytes to 25,200 with 62 per cent polymorphonuclear cells. Bronchoscopically aspirated fluid on Nov. 16, 1941 (corresponding to the roentgenogram in figure 4 *B*) contained a pure culture of nonhemolytic streptococci and (anaerobic) facultative streptococci. The lesion cleared rapidly

for two months after the situation shown in figure 4 *B* and gradually thereafter, leaving only a residual fibrosis almost two years later (fig. 4 *C*). The patient's condition was excellent, but she continued to have a few rales in the right cardiophrenic area and occasional bouts of slight fever and cough. On culture the gastric contents were not found to contain tubercle bacilli. The bronchogram (fig. 5 *A* and *B*) made two weeks after the roentgenogram in figure 4 *C* showed extensive bronchiectasis.

CASE 4.—When this Negro girl (S. S.) was first seen at 2 years of age because of contact with tuberculosis, she gave a positive reaction to a tuberculin test, and she had a history of noisy breathing and of frequent epistaxis for some time previously. A roentgenogram at this time showed slight fibrosis above the middle of the left lung. She was followed in the clinic with regular roentgenologic examinations.

When 9 years old, she again began to have frequent epistaxis and to go downhill. Roentgenologic examination showed enlargement of the lymph nodes at the root of the left lung and small areas of parenchymal infiltration in the apical region and in the third costal interspace on the left. Cultures of gastric and stool material were negative. The breath sounds were subdued, and the resonance was decreased in this area. There was no wheezing or rales. The temperature was 101 F. on admission, and some fever continued for a month. No cough was present. There was no gain of weight that month, but the second month she experienced a 4½ pound (2.3 Kg.) gain and had no fever. Her mother took her home from the sanatorium after two months.

Nine months after leaving the sanatorium, she was readmitted with far advanced disease. Direct smear of the sputum revealed tubercle bacilli repeatedly. Bronchoscopic examination nine days after readmission showed profuse secretions in the left main bronchus and some redness in the vicinity of the orifice of the upper lobe bronchus. Pneumothorax was started but was given up as ineffective. She had bronchogenic spread to other parts of the left lung as well as to the right. Two and a half months after her readmission a series of pulmonary hemorrhages began and led to her death about one month later. Injection of the lungs post mortem showed bronchiectasis in the upper lobe of the left lung in the area of fibrosis first seen when she was 2 years old.

SYMPTOMS

There were two groups of symptoms, namely, those representing the primary complex and the obstruction and those connected with the ectasis which later developed. In the first group symptoms varied. The most common and consistent symptom was wheezing; cough, expectoration, bouts of fever and at times acute illness with high fever also presented themselves. But these symptoms disappeared with the clearing of the pneumonitis and tuberculosis. Symptoms referable to clinical bronchiectasis, namely, repeated attacks of pneumonitis, hemoptysis, recurrent "colds" with fever, cough and expectoration of large amounts of sputum, occurred in few of the children and in a high degree in only one. For this patient, pneumonectomy was recommended. In the other children the dilatation was essentially without symptoms or indications of classic bronchiectasis.

TREATMENT

Tuberculous children with these bronchial complications need treatment for the infection, but they likewise need prophylactic attention if bronchiectasis is to be prevented. The fact that prolonged obstruction of a bronchus is so commonly followed by bronchiectasis points to the importance of attention to such conditions in order to prevent such sequelae. It is impossible to remove a large lymph node which encroaches on the lumen from without, but efforts can be made to facilitate drainage. This can be done by (1) steam inhalations to bring secretions to the optimal degree of thinness for normal ciliary functioning; (2) judicious use of theophylline ethylenediamine, and (3) posturing. If the child is old enough to allow posturing, the latter should be so arranged that the patient spends several hours several times a day in the prone and supine positions and on the two sides. It should be stressed that drainage is most facile when the position of the patient allows the involved bronchopulmonary segment to be uppermost, for in this way drainage becomes dependent and direct. Alternation of posture, however, is desirable to prevent restlessness and to prevent passage of secretions to pendant portions of the lung. In addition it is sometimes helpful to elevate the foot of the bed. This is especially true of very young children and is progressively less necessary with older children. Such treatment often prevents obstruction from becoming complete, because unrelieved sputum frequently is sufficient to plug the lumen already made narrow by disease or encroachment. In cases in which tuberculoma obstructs, bronchoscopic removal will often terminate the obstruction and contribute materially to restoration of normal function. When there is tuberculous granulation tissue or ulceration, topical application of silver nitrate through the bronchoscope aids in producing desirable results. Treatment is important intrinsically and prophylactically. The optimal care ordinarily given the tuberculous child is obviously indicated in these children, but in caring for such a tuberculous child one shies away from taking measures to collapse the lung for fear of making complete a partial obstruction.

COMMENT

The fact that such manifest bronchial dilatation existed in these 24 children for a considerable time with relatively few symptoms of bronchiectasis is frankly puzzling, and one can but wonder whether silent bronchiectasis is common, whether years may be required before symptoms develop and, finally, whether bronchiectasis of this segmental type and of the origin here described commonly causes symptoms or is actually of much clinical importance.

When lesions of this type develop in a bronchus (or a branch bronchus) tributary to a primary tuberculous focus, drainage of the diseased

area is no longer adequate. The trapped infection, continuing its activity for a longer or a shorter time, elaborates secretions which may eventually fill the bronchi and the parenchyma. It is possible (1) that the tuberculous disease actually invades the bronchi in a wide area of their extent, (2) that secondary infection affects these structures, (3) that the mechanical increase in fluid causes prolonged stretching of the bronchi with trophic changes or (4) that all of these factors in their varying relationships may explain the issue. There is good evidence in the work by Tannenberg and Pinner [6] that, in the production of experimental bronchiectasis, infection is an absolute prerequisite. It seems reasonable to assume that conclusions from such a demonstration as this could be applied to bronchiectasis in human beings.

Bronchiectasis occurs in an unusually large number of children having pulmonary tuberculosis. Prolonged bronchial obstruction appears to produce disease of the tissues involved in the bronchopulmonary segment or lobe tributary to the obstruction. From this point of view the complication called atelectasis in the former paper [4] might more properly be designated as obstructive pneumonitis.

Some one may assert that absolute proof has not been presented to show that bronchial obstruction from tuberculosis predisposes to or causes the ectasis. One doubts that all these children could have had nonclinical bronchiectasis prior to their infection with tuberculosis, which in every instance was located in the segment or lobe having the bronchiectasis, or that the tuberculous infection could have involved lymph nodes in such a way as to produce constant encroachment on the lumen of assumed preexisting dilated bronchi. It seems unlikely that, in the children described in the first study,[4] tuberculosis could have developed always in an area of the lung previously involved with bronchiectasis, especially when three fourths of all in the series for whom bronchograms were made revealed bronchial obstruction, partial or complete, from tuberculous disease. The likelihood seems so remote as to warrant dismissal. It has been shown, especially recently, by Baum and Amberson [7] that tuberculosis is sometimes superimposed on bronchiectasis. They have pointed out that tuberculosis appeared in 32 of their patients with known preexisting bronchiectasis—that in 9 instances it developed in a bronchiectatic lobe and in 23 in uninvolved lobes. Their patients were all adults.

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6. Tannenberg, G., and Pinner, M.: Atelectasis and Bronchiectasis: Experimental Study Concerning Their Relationship, J. Thoracic Surg. **11**:571 (Aug.) 1942.

7. Baum, O. S., and Amberson, J. B., Jr.: Nontuberculous Pulmonary Infections Complicating Pulmonary Tuberculosis, Am. Rev. Tuberc. **45**:243 (March) 1942.

Eighty-five of 712 children admitted to a tuberculosis sanatorium have shown signs of what might be termed obstructive pneumonitis. Forty-two of them underwent bronchoscopic examination, and 31 of these showed intrabronchial or extrabronchial tuberculosis which produced some degree of obstruction. Follow-up of these and similar cases revealed bronchiectasis in 70 per cent of the patients—a surprisingly large number. If this is the state of the patients, then tuberculosis must loom large as an etiologic factor in bronchiectasis.

SUMMARY

Pulmonary tuberculosis in children is frequently complicated by tuberculosis of a bronchus.

The bronchial disease may be present as granulomatous tissue (tuberculoma), as ulcer or merely as edema and inflammation. Tuberculous tracheobronchial lymph nodes often encroach on the lumen by pressing and at times eroding the bronchial wall.

Bronchial lesions such as those described are frequently associated with obstructive pneumonitis.

A large per cent of children who have shown obstructive lesions associated with tuberculosis of a bronchus reveal bronchiectasis in the segment or lobe involved in the obstruction. The dilatation extends from root to periphery.

In this study 37 children with known, proved obstructive lesions of the type described were recalled at a mean of 3½ years after the pulmonary lesions secondary to bronchial obstruction had cleared.

Bronchographic studies were made on the 37 children.

Iodized poppyseed oil 40 per cent could not be placed in the previously involved areas in 3 children. Of the 34 others, however, obvious signs of bronchiectasis were unequivocal in 24, or 70 per cent.

Pulmonary tuberculosis in children appears to be a common cause of bronchiectasis. Few of the 24 children with bronchiectasis presented conspicuous symptoms. Pneumonectomy was advised for 1 child.

Dr. W. M. Tuttle and Dr. Paul V. O'Rourke, who are on the consulting staff, did the bronchoscopic examinations from which a large part of the evidence for this work was obtained.

Case Reports

PERIARTERITIS NODOSA COMPLICATING SCARLET FEVER

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SINCE the description of periarteritis nodosa by von Rokitansky [1] in 1852 and by Kussmaul and Maier [2] in 1865, numerous reports have appeared in the literature. Dickson [3] and subsequent observers favored the designation of polyarteritis nodosa, since the inflammatory reaction is not confined to the adventitial or periadventitial tissues. This term is probably more adequate in describing the morphologic characteristics of the disease, although since the etiologic factors are still under consideration, primary arteritis in the sense implied by Karsner [4] of an arteritis in which the infective organisms are not demonstrated warrants consideration.

The cause of this disease has been and is a much debated point, although some are of the opinion that a filtrable virus is the causative agent.[5] Syphilis at one time had been suspected but this view has been entirely discarded. Spiro [6] expressed the opinion that it was a

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1. von Rokitansky, G.: Ueber einige der wichtigsten Erkrankungen der Arterien, Denkschr. d. k. Akad. d. Wissensch. **4**:49, 1852.

2. Kussmaul, A., and Maier, R.: Ueber eine bisher nicht beschriebene eigenthümliche Arterienerkrankung (periarteritis nodosa), die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellähmung einhergeht, Deutsches Arch. f. klin. Med. **1**:484, 1866.

3. Dickson, W. E. C.: Polyarteritis Acuta Nodosa and Periarteritis Nodosa, J. Path. & Bact. **12**:31, 1907.

4. Karsner, H. T.: Primary Inflammation of Arteries, Ann. Int. Med. **11**: 164, 1937.

5. (*a*) Harris, W. H., and Friedrichs, A. V.: Periarteritis Nodosa with a Classification of the Pathology, J. M. Research **43**:285, 1922; The Experimentation Production of Periarteritis in the Rabbit with a Consideration of the Specific Causal Excitant, J. Exper. Med. **36**:219, 1922. (*b*) von Haun, F.: Patho-histologische und experimentelle Untersuchungen über Periarteritis nodosa, Virchows Arch. f. path. Anat. **227**:90, 1919.

6. Spiro, P.: Zur Kenntnis des Wesens der Periarteriitis nodosa, Virchows Arch. f. path. Anat. **227**:1, 1919.

form of postinfectional mesarteritis of varying causation and Gruber [7] postulated that it was a disease of toxic-infectious origin without a specific cause. Bennett and Levine,[8] as well as Wolbach [9] and Wolbach and Todd and Palfrey,[10] have pointed out the similarity between the lesion in periarteritis and that in typhus and in Rocky Mountain spotted fevers. Harris and Friedrichs [5a] and von Haun [5b] have succeeded in producing similar changes in lower animals, and the finding of a similar diseases in the lower animals (calf, swine, dog and deer) points to the specific infectious nature of the disease. The streptococci found and the relationship of this disease to rheumatic fever have been studied.[11] Cohen, Kline and Young [12] expressed the opinion that it was a manifestation of clinical allergy of severe degree, and subsequent reports [13] appear to favor the allergic nature of this disease. Sepsis has also been regarded as a causative factor, and this opinion has received considerable support.[14]

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7. Gruber, G. B.: Zur-Frage der Periarteritis nodosa, mit besonderer Berücksichtigung der Gallenblasen und Nieren-Beteiligung, Virchows Arch. f. path. Anat. **258**:441, 1925; Kasuistik und Kritik der Periarteritis nodosa, Zentralbl. f. Herz- u. Gefässkr. **18**:145, 1926.

8. Bennett, G. A., and Levine, S. A.: Two Cases of Periarteritis Nodosa, One with Unusual Manifestations (Meningeal Form), Am. J. M. Sc. **177**:853, 1929.

9. Wolbach, S. B.: Studies on Rocky Mountain Spotted Fever, J. M. Research **41**:1, 1919.

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12. Cohen, M. B.; Kline, B. S., and Young, A. M.: The Clinical Diagnosis of Periarteritis Nodosa, J. A. M. A. **107**:1555 (Nov. 7) 1936.

13. Berger, S. S., and Weitz, M. A.: Periarteritis Nodosa: Case Report, J. Allergy **9**:489, 1938. Weir, D. R.: Polyarteritis Nodosa, Am. J. Path. **15**:79, 1939. Periarteritis Nodosa, Cabot Case 25141, New England J. Med. **220**:600, 1939. Motley, L.: Periarteritis Nodosa with Report of Case Showing Unusual Features and Apparent Recovery, J. A. M. A. **106**:898 (March 14) 1936.

14. Haining, R. B., and Kimball, T. S.: Polyarteritis Nodosa, Am. J. Path. **10**: 349, 1934. Rothstein, J. L., and Welt, S.: Periarteritis Nodosa in Infancy and Childhood: Report of Two Cases in the Literature, Am. J. Dis. Child. **45**:1277 (June) 1933. Moschcowitz, E.: The Nosological Status of Periarteritis Nodosa, J. Mt. Sinai Hosp. **5**:337, 1938. Goldstein, I., and Wexler, D.: Bilateral Atrophy of the Optic Nerve in Periarteritis Nodosa, Arch. Ophth. **18**:767 (Nov.) 1937.

Arkin [15] has divided the disease into four stages: first, the degenerative stage; second, the acute inflammatory stage; third, the granulation tissue stage; fourth, the healed granulation tissue stage. The inflammatory reaction is characterized by necrosis of the medial coat of the small and medium-sized muscular type of vessels with fibrinous exudation. Shortly thereafter there is noticeable cellular infiltration and formation of granulation tissue in and about the arterial wall together with varying degrees of intimal proliferation. The complicating factors in the arteries are formation of aneurysms, thrombosis and hemorrhage. The organs most commonly involved are the kidneys, heart, liver, muscle, peripheral nerves and gastrointestinal tract. The central nervous system is involved in about 8 per cent or more of the cases, according to the literature, as pointed out by Kernohan and Woltman,[16] but it is rarely involved when the patients are children. However, any or every organ of the body may be affected.

Clinically this disease is difficult of diagnosis, and even at gross postmortem examination at times the nodular protuberances of the vessels cannot be ascertained; it is only after microscopic study that the lesions of the vessels are demonstrated. The presence of eosinophilia with peculiar symptoms and with leukocytosis may be of diagnostic aid, as pointed out by Lebowich and Hunt [17] and by previous investigators. A bizarre clinical picture of septic temperature, polyneuritis, hematuria or nephritis, abdominal cramplike pains and progressive emaciation are the usual clinical findings. The disease occurs among children and adults, the range of age being from 3 months to 78 years. The majority of the instances, however, have been seen in adults. In our case the disease occurred in an 11 year old boy.

REPORT OF A CASE

C. H., an 11 year old boy, was admitted to the Philadelphia Hospital for Contagious Diseases on March 4, 1942, with a chief complaint of convulsions. The family history was noncontributory. The boy had suffered no illnesses in the past excepting measles and pertussis. He did have a history of allergy as evidenced by hives following the ingestion of tomatoes. His present illness began on Feb. 8, 1942, when a sore throat, nausea and vomiting developed, followed twenty-four hours later by a generalized punctate erythematous rash. A diagnosis of typical scarlet fever was made by his family physician. Convalescence was uneventful, and the child was allowed out of bed on Feb. 26. The next day, almost three weeks after the onset of the scarlet fever, he began to

15. Arkin, A.: A Clinical and Pathological Study of Periarteritis Nodosa, Am. J. Path. **6**:401, 1930.

16. Kernohan, J. W., and Woltman, H. W.: Periarteritis Nodosa: A Clinicopathologic Study with Special Reference to the Nervous System, Arch. Neurol. & Psychiat. **39**:655 (April) 1938.

17. Lebowich, J., and Hunt, H. D.: The Diagnostic Significance of Eosinophilia in Periarteritis Nodosa, Am. J. Clin. Path. **10**:642, 1940.

vomit and to complain of abdominal pain and of pain in the ankles and wrists. Red blotches appeared on the face, and he had "itching lumps all over." The next day the right ankle became swollen and painful. Within three days vomiting had ceased and the pain in the ankle had subsided. On March 3 the patient complained of severe headache, of vertigo, and of being unable to move his right hand and arm. He was extremely drowsy and at times appeared irrational. On March 4, the day of admission, he complained that his feet felt "funny" and that he could not "feel the floor." Shortly after this he had a generalized convulsion and was rushed to the hospital.

Physical Observations.—The significant physical findings at the time of the patient's admission consisted of semistupor, internal strabismus of the left eye and spastic paralysis of the left upper and lower extremities. Although the knee jerks were absent, the achilles reflex was active. No Babinski sign was present. The spleen was readily palpable 4 cm. below the costal margin. During the examination the boy had another convulsion, involving the abdominal muscles and those of the lower part of the right leg. The head and eyes were drawn to the left. The temperature was 102 F. The pulse rate was 130, the respiratory rate 32 and the blood pressure 110 systolic and 70 diastolic. The eyegrounds showed mild attenuation of the most peripheral retinal arterioles plus some of the small branches. The blood urea nitrogen was 91 mg. per hundred cubic centimeters. A complete blood count was not remarkable except for a leukocyte count of 27,520 per cubic millimeter, with 87 per cent neutrophils, 12 per cent lymphocytes and 1 per cent eosinophils. Cultures of material from the nose and throat yielded no hemolytic streptococci. Although the spinal fluid at the time of the patient's admission was clear, eight hours later it was grossly bloody, uniformly so in three specimens of the fluid withdrawn. It was assumed that rupture of a pial vessel had occurred during the convulsive movements. The boy became progressively worse. Urine obtained after a twenty-four hour period of anuria showed red blood cells and a heavy cloud of albumin. The blood urea nitrogen rose steadily to 191 mg. per 100 cubic centimeters and "urea frost" developed. The blood pressure rose to 150 systolic and 110 diastolic as the stupor deepened. On his fourth hospital day, the patient's temperature rose steadily to 108 F.; at this point pulmonary edema developed and he died. The clinical diagnosis was convalescent scarlet fever, scarlatinal nephritis, uremia and subarachnoid hemorrhage.

Findings at Autopsy.—External examination of the body revealed nothing of gross pathologic significance other than a moderate amount of bloody fluid coming from the nose and mouth and moderate dilatation of the left external abdominal ring. No nodules could be palpated along the course of the peripheral vessels, and there were no cutaneous hemorrhages.

Abdomen: Internal inspection of the abdominal cavity revealed an enlarged liver which extended 1½ fingerbreadths below the right costal margin and several areas of macular hemorrhage along the edge of the greater omentum.

Chest: Internal inspection of the thoracic cavity showed some enlargement of the thymus, although there was no evidence of compression of the great vessels at the root of the neck. The heart was normal in size and position, and its pericardial cavity contained the normal amount of clear amber-colored serous fluid. Both pleural sacs contained a small amount of blood-tinged fluid.

Heart: The heart on gross inspection was relatively normal except for cloudiness of the epicardial surface and some loss of the normal color and consistency of the myocardium. It weighed 200 Gm. The aorta was healthy throughout, except for a few tiny yellow plaques on the intimal surface near the aortic valve.

Lungs: The lungs were emphysematous in their upper lobes. The lower lobes were firmer than normal and felt moist on palpation. Through the pleural surfaces areas of macular hemorrhage, varying from 1 to 4 cm. in diameter, were visualized. These areas of hemorrhage were confined for the most part to the posterior dependent portions of the lower lobes, although a few were seen in the apical and basal portions of the upper lobe of the right lung. Cut sections confirmed the findings of macular hemorrhage, and in addition they showed edema and congestion. The bronchial mucosa was congested throughout, and its lumen was free of exudate. The left lung weighed 250 Gm. and the right lung 400 Gm.

Liver: The liver had the parboiled appearance of cloudy swelling and pale yellow, greasy areas of fatty metamorphosis. The weight was 1,450 Gm. The gallbladder and bile ducts were grossly healthy.

Spleen: The spleen showed the mushy, pultaceous softening of toxic alteration. It weighed 110 Gm.

Adrenal Glands: The adrenal glands were normal in size and position and on sectioning disclosed the mild to moderate cystic softening of postmortem degeneration. There was no evidence of parenchymal hemorrhage.

Kidneys: Both kidneys were heavier than normal; the left weighed 210 Gm., and the right weighed 250 Gm. They were enlarged, swollen and somewhat flabby. The capsules were thin and peeled away readily from smooth, pale surfaces showing injection of the stellate veins and occasional petechial hemorrhage. A cut section disclosed a pale, swollen, moderately soft parenchyma. The gross picture suggested severe toxic nephrosis rather than acute glomerulonephritis. On examination of the pelvic mucosa massive hemorrhage bilaterally was displayed. The ureters were healthy except for serosal injection. The urinary bladder contained a small amount of cloudy urine. The mucosal surface in the region of the urethral orifice had several areas of recent macular hemorrhage with edema of the surface, which in one area assumed a polypoid appearance.

Gastrointestinal Tract: Examination of the entire tract revealed postmortem autolysis (the autopsy was performed nineteen and one-half hours after death). The stomach was distended with brownish black fluid. Examination of the mucosal surface of the small bowel showed lymphoid hyperplasia and areas of macular hemorrhage. The mesenteric nodes revealed mild enlargement.

Pancreas: The pancreas was grossly normal.

Brain: There was moderate edema of the subcutaneous tissues of the skull, and in the left parietal region there was an area of hemorrhage measuring 1.5 cm. in diameter. This hemorrhage was present in the subcutaneous fat and in the muscular tissues but not in the corium and the epidermal layer. There was no gross evidence of fracture of the skull or of epidural or subdural hemorrhage. The brain was heavy, congested and edematous, weighing 1,450 Gm. The convolutions of the left side were flattened. In the superior portion of the left frontoparietal region there was an area of softening. Coronal sections through this same area disclosed an area of hemorrhage extending about 1 cm. from the anterior pole of the frontal lobe to the midportion of the parietal lobe, with rupture into the lateral ventricle. This area measured about 3.5 cm. in diameter. It was cystic in appearance, being filled with blood clot surrounded by a wide rim of soft yellow, degenerating brain tissue. There was a similar but smaller area of hemorrhage in the right parieto-occipital area and a still smaller focus in the left occipital lobe. The meninges were of normal thickness.

We have presented the clinical and gross observations at autopsy in detail, feeling perhaps that from the bizarre clinical picture and the several, scattered

areas of hemorrhage throughout the body we might have suspected the correct diagnosis at autopsy despite the absence of definite nodulations along the course of the vessels.

Fig. 1.—Section of the fatty capsule of the adrenal gland showing necrotizing arteritis and perivascular inflammatory reaction.

Microscopic Observations.—Microscopic study disclosed the true nature of the process. Examination of the cardiac slides revealed an acute interstitial and perivascular inflammatory cellular infiltration and a moderate degree of myocardosis.

In the adventitial fat of the ascending aorta there was a medium-sized blood vessel showing complete necrosis of its wall, with replacement by suppurative exudate. The intima appeared to be intact. The exudate spread out into the periadventitial tissues and extended for a short distance into the tunica media of the aorta.

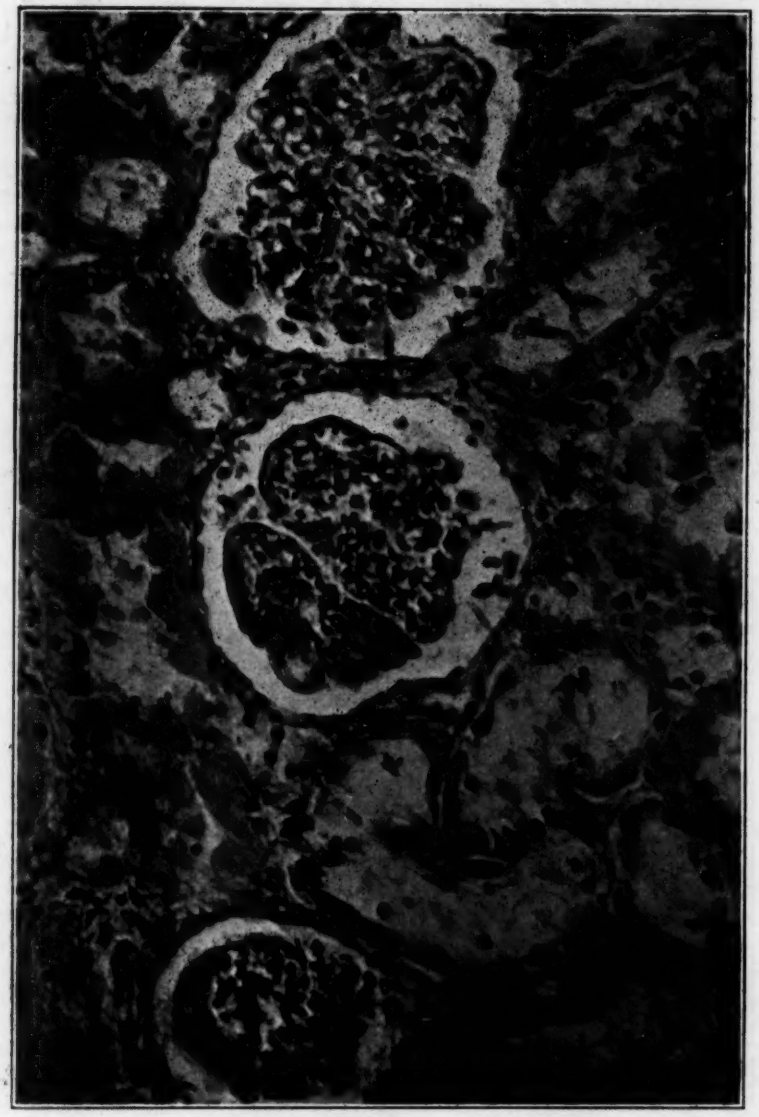

Fig. 2.—Section of the kidney showing the extensive tubular degeneration and the hyaline thrombi in the glomerular capillaries.

The lungs showed deep congestion, edema, interstitial inflammatory reaction, hemorrhage into the alveolar spaces and patchy areas of bronchopneumonic consolidation, with early organization. The large vessels revealed edema and

fibrinoid exudate in their walls but no necrosis. Around the smaller vessels of one of the large bronchial branches there was an acute edematous and suppurative reaction, but here again the intimal lining cells were intact.

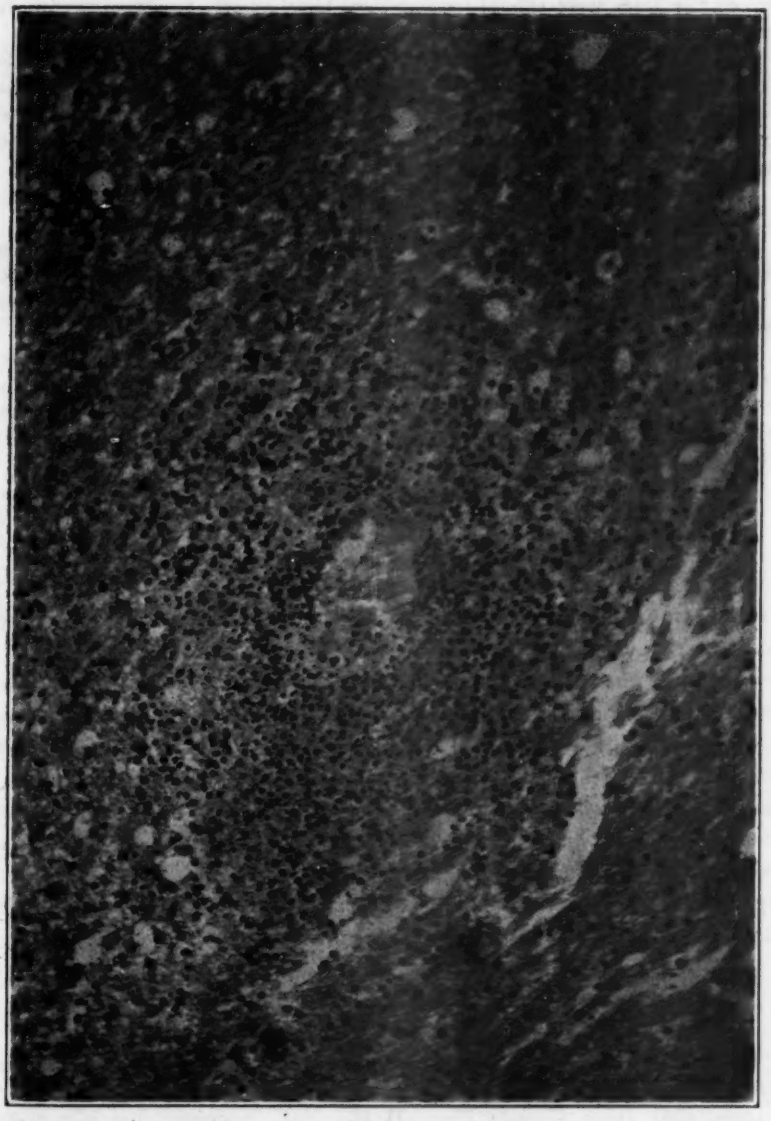

Fig. 3.—Microscopic section of the brain showing a small vessel whose wall is totally necrotic and infiltrated by neutrophils in varying stages of degeneration.

The liver exhibited acute congestion, granular degeneration and swelling of the parenchymal cells and an occasional focal aggregation of mononuclear cells

around the small vessels of the portal areas. This is the type of reaction that Smith, Morgan and Mudd [18] have reported in generalized streptococcic infections.

The spleen revealed congestion, degenerative changes in the germinal centers and focal patches of inflammatory cellular infiltration immediately beneath the capsule. The parenchymal cells of the adrenal glands were healthy, but in the fatty capsule there were several medium-sized blood vessels disclosing necrotizing arteritis (fig. 1).

The kidneys showed definite tubular degeneration and acute exudative glomerulonephritis, with hyaline thrombi in many of the glomerular tufts. Occasional hyaline casts filled the lumens of the tubules. In the pelvic region were revealed numerous small and medium-sized vessels showing necrotizing and suppurative arteritis, with extensive hemorrhage into the subepithelial layers (fig. 2).

The wall of the urinary bladder was greatly thickened by edema and by a suppurative exudate which was found in relation to necrosed vessels.

The omental fat, the submucosa of the ileum, the thymus and the subcutaneous tissues of the parietal scalp showed the presence of similar arteritis and arteriolitis.

Examination of the pancreas revealed interstitial edema, early postmortem autolysis and necrotizing arteritis in its surrounding fatty tissue.

The brain had areas of degeneration and hemorrhage. The medium-sized and the small blood vessels showed a necrotizing suppurative process throughout the wall, with extension into the periadventitial tissues. The meninges were thickened by edema, and around an occasional vessel there was a scant infiltration by inflammatory cells (fig. 3).

In summary, on histologic study practically all of the organs presented evidence of periarteritis nodosa.

COMMENT

We feel that this case is of interest because of the patient's age, the association with scarlet fever and possibly because of the history of food allergy.

Gruber [7] has considered periarteritis nodosa as a hypersensitive reaction occurring in a variety of infectious-toxic diseases, with gonococcic endocarditis and meningococcic meningitis mentioned specifically. Cohen, Kline and Young [12] have expressed the opinion that it is a manifestation of clinical allergy of severe degree. Rich [19] has reported several cases associated with serum sickness and with hypersensitive reactions to sulfonamide compounds, and Rich and Gregory [20] have experimentally reproduced typical periarteritic lesions in rabbits by establishing conditions analogous to serum sickness in the human being.

18. Smith, L. W; Morgan, I. M., and Mudd, S.: Histopathological Changes Produced in Rabbits by Experimental Inoculation with Hemolytic Streptococci, Certain of Their Component Factors and Saponin, Am. J. Path. **16**:87, 1940.

19. Rich, A. R.: The Role of Hypersensitivity in Periarteritis Nodosa, as Indicated by Seven Cases Developing During Serum Sickness and Sulfonamide Therapy, Bull. Johns Hopkins Hosp. **71**:123, 1942; Additional Evidence of the Role of Hypersensitivity in the Etiology of Periarteritis Nodosa, ibid. **71**:375, 1942.

20. Rich, A. R., and Gregory, J. E.: The Experimental Demonstration That Periarteritis Nodosa Is a Manifestation of Hypersensitivity, Bull. Johns Hopkins Hosp. **72**:65, 1943.

In 3 of the 14 cases reported by Jones [21] there was a history of allergy. Recently, Reiman, Price and Herbut [22] reported 2 cases associated with trichinosis and suggested that Trichinella spiralis may serve as one of the causes of periarteritis nodosa. It would appear, then, that this symptom complex may represent an allergic manifestation of varied causation, and we feel that our case further supports this assumption. Our patient had manifested an allergy to one type of food, namely tomatoes, and after the third week of scarlet fever periarteritis nodosa developed at a time when the formation of antibodies is known to reach its peak and when "scarlatinal nephritis," which is rather generally believed without conclusive proof to be an allergic type of response to hemolytic streptococcic products rather than to direct bacterial infection, commonly occurs. It is at a time, too, when it is impossible to demonstrate hemolytic streptococci in the lesions. All of these factors, we feel, point to an allergic type of reaction. Since the boy had an allergic background to begin with, and since we also believe that scarlatinal nephritis is an allergic manifestation, it is difficult to say which of these factors is the more important one.

It is interesting to note that the case described in this paper was associated with acute exudative glomerulonephritis in addition to tubular and vascular changes. This association had previously been noted by Hoyne and Steiner [23] in a child having scarlet fever, nephritis, periarteritis nodosa and polyneuritis. Dr. Warren Hunter [24] of the University of Oregon gave us the opportunity of seeing the slides from a case he is reporting elsewhere which is very similar to ours both as to the development of periarteritis following scarlet fever and as to histopathology.

SUMMARY

Periarteritis nodosa followed scarlet fever in a boy of 11. The vascular lesions were widely distributed throughout the organs of the body and did not produce gross evidence of nodulations, although numerous petechial and macular hemorrhages were visualized grossly. The patient died of intracerebral hemorrhage and of renal failure. We feel that this case lends support to the assumption that periarteritis nodosa may be an allergic manifestation of varied causation. In our case the allergic state probably resulted from hemolytic streptococci or their products.

21. Jones, G. M.: Periarteritis Nodosa with Case Reports, Ann. Int. Med. **16**:920, 1942.

22. Reiman, H. A.; Price, A. H., and Herbut, P. A.: Trichinosis and Periarteritis Nodosa: Differential Diagnosis; Possible Relationship, J. A. M. A. **122**: 274 (May 29) 1943.

23. Hoyne, A. L., and Steiner, M. M.: Periarteritis Nodosa Complicating Scarlet Fever with Unusual Syndrome of Nephritis and Polyneuritis, Am. J. Dis. Child. **59**:1271 (June) 1940.

24. Hunter, W.: Personal communication to the authors.

HEMOLYTIC DISEASE OF THE NEWBORN (ERYTHROBLASTOSIS FETALIS)

Treatment by a Single Massive Transfusion, with Complete Recovery

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INFANTS with hemolytic disease of the newborn (erythroblastosis fetalis) receiving transfusions of Rh-negative blood have been shown to have a normal survival of the transfused Rh-negative cells, but when they are given transfusions of Rh-positive cells a rapid destruction of those cells occurs.[1] In addition there seems to be some slowing down of the rate of hemolysis of the infant's Rh-positive cells when the transfusion is with Rh-negative blood, whereas this does not occur when a transfusion of Rh-positive blood is given. The present case report of an infant with hemolytic disease of the newborn who received an accidental massive transfusion of Rh-negative blood is offered as shedding some light on the presence of an anti-Rh antigen-antibody reaction factor in Rh-negative blood.

REPORT OF A CASE

C. D. F., a boy weighing 8 pounds 13 ounces (3,997 Gm.), was delivered by cesarean section at St. Joseph's Infirmary, Houston, Texas, approximately eighteen days before term. The mother, 42 years of age, tripara and quadrigravida, was admitted to the hospital on Nov. 20, 1945, and was delivered the following day under spinal anesthesia. The present pregnancy had been uneventful with the exception of the mental anguish of the mother, who feared that the pregnancy might terminate as had the two previous ones.

The first pregnancy terminated in April 1935 with the delivery of a 7 pound 11 ounce (3,487 Gm.) boy, whose blood was discovered later to be Rh-positive, group A. The second pregnancy ended in July 1936 with the delivery of a 6 pound 10½ ounce (3,019 Gm.) boy asphyxiated at birth and requiring artificial respiration. Respirations and heart action ceased after seven hours and a roentgenologic examination of the chest before death showed considerable atelectasis. The infant had received an injection of 30 cc. of whole blood intramuscularly. The third pregnancy, producing a 6 pound 12 ounce (3,062 Gm.) boy terminated in November 1937 after eight months of gestation by cesarean section, because of placenta previa totalis. The infant was in good condition at birth, but after two and a half hours in the nursery suddenly became cyanotic and began to gasp for breath. Thirty cubic centimeters of whole blood was injected into the buttocks, and the infant was placed in a respirator and given oxygen. Breathing continued to be labored and the heart action ceased after twelve hours. Again, an autopsy was not performed.

When the patient became pregnant for the fourth time a test for the Rh factor was done on her and her husband. Her blood was found to be Rh negative, group O. The husband's was found to be Rh positive, group A. In view of the previous experience and the past history, the obstetrician decided to terminate the pregnancy two weeks before term in the hope of getting a viable infant with a minimal amount of erythroblastotic damage. This procedure, as stated previously, was carried out at an appointed time.

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1. Mollison, P. L.: The Etiology of Erythroblastosis Fetalis and Certain Haemolytic Transfusion Reactions with Special Reference to the Rh Factor, Proc. Roy. Soc. Med. **36**:221, 1943.

On delivery the infant cried immediately, but was a little pale in color and slightly edematous. The amniotic fluid showed no staining, and the umbilical cord was normal though rather large. Rh-negative donors (groups A and O) had been called for immediate cross matching. This cross matching was made with blood from the infant's umbilical cord. The blood from the umbilical cord was found to belong to group A. The Rh factor was positive but not strongly so. The cord blood was cross matched with that of the Rh-negative (group A) donor.

The following blood studies were made from the umbilical cord blood. The hemoglobin content was found to be 80 per cent; the red cells, 5,130,000; the white cells, 10,300 with 2 per cent erythroblasts, 36 per cent small lymphocytes, 2 per cent large lymphocytes, 1 per cent large mononuclear leukocytes and 43 per cent neutrophils. There were 11 per cent eosinophils, 2 per cent myelocytes, 4 per cent stab cells and 1 per cent juvenile forms. The blood sugar content was 75 mg. per hundred cubic centimeters, the globulin 2.45 Gm., the albumin 3.00 Gm. and the total protein 5.45 Gm. The albumin-globulin ratio was 1.2 to 1.

A needle was placed in the internal saphenous vein at the left ankle, and a transfusion of 90 cc. of Rh-negative blood belonging to group A was given three hours after birth. Nine hours after birth the infant received 50 cc. of whole plasma. A determination of hemoglobin six hours after the initial transfusion showed a value of 105 per cent. The infant seemed to be in excellent condition. The night passed uneventfully, a little mucus being passed from the infant's mouth.

By the following morning the original needle used in transfusion had become stopped up; therefore another needle was inserted into the vein of the other ankle and a second transfusion of 90 cc. of blood ordered from what was left of the 400 cc. taken from the donor the previous day. After a few cubic centimeters had run in, there was a stoppage of this transfusion also, and a house doctor was called. Neither the nurse nor the house doctor could start the flow of blood again. Then, inadvertently, both left the infant alone with the cutoff on the transfusion tubing open. When the nurse returned a short time later, the entire amount of blood in the transfusion flask, an estimated 310 cc. had run in. The infant became quite red and started perspiring freely. He had been a little edematous up to this time, but now the edema was practically replaced by sclerema. He was placed in an oxygen box and observed most carefully and with considerable anxiety. He spent a comfortable afternoon and night and took fluids well by mouth. During the following days a number of blood counts were made and are recorded in the table.

The infant's condition remained good during the ten days before discharge from the hospital. He took his feedings well and acted normally. At no time did any icteric tinge appear in his skin. The infant's blood at discharge had a strongly positive reaction for the Rh factor whereas at birth the reaction was only weakly positive. His weight at discharge was 8 pounds 13½ ounces (4,011 Gm.).

COMMENT

There is some evidence that anti-antigen-antibody reaction factors are present in the blood. Polayes,[2] in 1928, concluded from a study of cord, fetal and maternal bloods that there is an interchange of antigens and antibodies between the mother and the fetus through the placenta, but that by some "protective mechanism" pathologic effects are prevented. The nature of this "protective mechanism" was

2. Polayes, S. H.; Lederer, M., and Wiener, A. S.: Studies in Isohemagglutination: II. The Landsteiner Blood Groups in Mothers and Infants, J. Immunol. **17**:545, 1929.

Blood Counts of C. D. F. Before and Following the Massive Transfusion

Date	11/21, 8 A. M.	11/21, 5 P. M.	11/22. P. M.	11/23, A. M.	11/23, P. M.	11/24	11/25	11/26	11/27	11/28	11/30	12/21
Hemoglobin, per cent	80	105	123	138	145	148	148	130	135	128	135	122
Red blood cells, number	5,130,000	...	...	7,900,000	7,800,000	5,920,000	5,680,000	6,940,000	7,300,000	7,540,000	7,000,000	6,450,000
White blood cells, number	10,300	...	...	25,300	11,400	7,800	9,500	14,500	17,000	12,000	16,000	7,350
Erythroblasts, per cent	2	...	...	...	3							
Normoblasts, per cent	..	...	...	...	..	..	..	1				
Lymphocytes, per cent												
Small	36	...	...	28	20	50	41	51	57	49	34	36
Large	2	...	...	...	3	..	4	..	..	4	1	
Large mononuclears, per cent	1	...	...	...	4							
Neutrophils, per cent	43	...	...	69	69	46	47	43	42	43	62	60
Stab cells, per cent	4											
Juvenile forms, per cent	1											
Eosinophils, per cent	11	...	...	3	4	4	8	5				

The first determination was made on cord blood; all others were made on peripheral blood obtained by stab wounds of the heel. The first transfusion was given at 11 a. m., November 21. The massive transfusion was received on the forenoon of November 22.

thought to be due to the fact that the antigens were circulating in the tissue fluids and could combine with their antibodies before pathologic effects were produced.

Landsteiner and Levine [3] found a high percentage of cold agglutinins in bloods which they tested and observed that this reaction persisted in 3 per cent of them at room temperature. The fact that 5 of their patients received transfusions of blood the cells of which were agglutinated at 20 C. and had no reaction suggests that heat can be an anti-antigen-antibody reaction factor. Cold agglutination may be only the result of removal of the heat anti-antigen-antibody reaction factor.

Boorman, Dodd and Mollison [4] have observed anti-Rh agglutinins in several erythroblastotic infants within a short time after birth. The only possible theoretic explanation for the anti-Rh agglutinins being present and not being combined with their antigenic Rh-positive red blood cells when there is an excess of the antigen is the presence of an anti-Rh antigen-antibody reaction factor.

Leonard [5] stated that infusion of plasma into certain erythroblastotic infants who are not anemic is preferable to infusion of whole blood. This should be true on the basis of an anti-Rh antigen-antibody reaction factor if the plasma is obtained from Rh-negative donors.

DeMarsh, Windle and Alt [6] have stated that the total volume of blood of the average newborn infant is between 250 and 350 cc. It is apparent, then, that the infant here reported on received more blood in a little over twenty-four hours than his estimated original total volume. At the end of nine days his Rh factor should have been less positive than at birth owing to the continued hemolysis of his Rh-positive cells by the anti-Rh agglutinins received from the mother,[7] leaving in his blood stream primarily the transfused Rh-negative red blood cells. As will be reported in another article,[8] the titer of the anti-Rh agglutinins in the serum of this mother was found to be 1:24 thirty days post partum. However, the infant had a strongly positive reaction for the Rh factor before discharge from the hospital, indicating that he had formed more Rh-positive cells than he had had at birth, or that at birth or soon thereafter he was under some dampening influence on the Rh antigen-antibody reaction. It is apparent, therefore, that the infant may have received some factor in the tremendous transfusion that inhibited or prevented the Rh antigen-antibody reaction. Further data on the existence of the anti-Rh antigen-antibody reaction factor are being reported in another article.[8]

The presence of such an anti-Rh antigen-antibody reaction factor in Rh-negative blood can explain many of the more obscure phenomena associated with erythroblastosis fetalis.

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3. Landsteiner, K., and Levine, P.: On the Cold Agglutinins in Human Serum, J. Immunol. **12**:441, 1926; On Issoagglutinins Reactions of Human Blood Other Than Those Defining the Blood Groups, ibid. **17**:1, 1929; On the Inheritance and Racial Distribution of Agglutinable Properties of Human Blood, ibid. **18**:87, 1930.

4. Boorman, K. E.; Dodd, B. E., and Mollison, P. L.: Clinical Significance of the Rh Factor, Brit. M. J. **2**:535, 1942.

5. Leonard, M. F.: Hemolytic Disease of the Newborn (Erythroblastosis Fetalis), J. Pediat. **27**:249, 1945.

6. DeMarsh, Q. B.; Windle, W. F., and Alt, H. L.: Blood Volume of the Newborn Infant in Relation of Early and Late Clamping of the Umbilical Cord, Am. J. Dis. Child. **63**:1123 (June) 1942.

7. Levine, P.: The Pathogenesis of Erythroblastosis Fetalis, J. Pediat. **23**: 656, 1943.

8. Data to be published.

First, the fact that a mother acquiring isoimmunization does not have reactions to the fetal antigen that may come through the placenta later in pregnancy, has never been explained. If in pregnancy a woman is capable of acquiring isoimmunization to the infant's Rh antigen that comes through the placenta, it would seem that later in the course of her pregnancy she should give the transfusion type of reaction to the same antigen that crosses the placental barrier. However, she does not give the transfusion type of reaction to such antigen. The presence of an anti-Rh antigen-antibody reaction factor in her blood could explain the failure of the reaction to develop. The simultaneous presence of antigen and antibodies has been observed in at least 2 Rh-negative persons in whom transfusion reactions developed.[9]

Second, the titer of the maternal anti-Rh agglutinins is not proportionate to the severity of the fetal disease. The reason for this lack of correlation between the severity of the disease in the fetus and the concentration of agglutinins in the mother's blood is stated by Potter [10] to be unknown. The presence of an anti-Rh antigen-antibody reaction factor can explain this phenomenon. Women whose infants are affected with the most severe form of the disease and in whom it is impossible to demonstrate agglutinins may have little or no anti-Rh antigen-antibody reaction factor, so that their infants receive no protection from them. In mothers having a high titer and a high neutralizing-Rh antigen-antibody reaction factor, the infant will be given considerable protection and may be very mildly affected.

Third, Levine [7] stated that one would expect erythroblastosis fetalis to be a disease exclusively of the fetus, with spontaneous cure at birth. The presence of an anti-Rh antigen-antibody reaction factor circulating in Rh-negative blood and holding this reaction in abeyance until the fetus is removed from its sphere of influence could explain the mechanism of the rapid development of erythroblastosis fetalis shortly after birth.

SUMMARY

The case of an infant with erythroblastosis fetalis, or hemolytic disease of the newborn, who accidentally received a massive transfusion equivalent to his theoretic blood volume is reported.

A complete suppression of the antigen-antibody reaction occurred and left the infant with a stronger Rh-positive reaction at the end of ten days than immediately after birth.

It is thought that an Rh-negative person has in his blood a suppressing (or anti-Rh) antigen-antibody reaction factor, and that this factor slows down or cushions the antigen-antibody reaction when it is present in sufficient quantities.

It is suggested that larger transfusions of Rh-negative blood, though not as large as in the present case, be given to infants with hemolytic disease of the newborn in an effort to use this anti-Rh antigen-antibody reaction factor and to bring the infant's blood concentration up to the normal average.

It may be feasible to use suitable Rh-negative serum during pregnancy in an effort to slow down or to prevent the development of hemolytic disease of the newborn (erythroblastosis fetalis) in utero.

It may be advisable to examine serums of Rh-negative donors for evidence of the anti-Rh antigen-antibody reaction factor.

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9. Levine,[7] p. 674.

10. Potter, E. L.: Present Status of the Rh Factor, Am. J. Dis. Child. 68:32 (July) 1944.

ACUTE HEMOLYTIC ANEMIA ASSOCIATED WITH AUTOAGGLUTINATION WITH A THERMAL AMPLITUDE OF 0 TO 37 C.

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AUTOAGGLUTINATION is defined as the agglutination of a person's red cells by his own serum, because of the presence of an absorbable agglutinin in the serum and a corresponding agglutinogen in the cells (Wiener [1]).

Although reports concerning clumping or sticking together of red cells, observed when counting red cells, go back as far as 1890 (Reitman,[2] Klein,[3] Ascoli [4] and others), it is not certain whether these authors dealt with true autoagglutination or with pseudoagglutination (rouleaux formation). The first comprehensive description of true autoagglutination was given by Landsteiner [5] (1903). He described the cold (auto) agglutinin as present in many normal serums, active at a temperature of 0 to 5 C. only and effective not only against the cells of the same person but also against each group of human erythrocytes and some groups of animal erythrocytes. The agglutination is reversible by warming and reappears in the cold; the agglutinins can be absorbed by the red cells and are released from them into the suspending fluid when warmed.

When transfusion of blood became a widely used therapeutic measure, autoagglutinins were observed which showed the characteristics previously described in all respects but one—they acted not only at the low temperatures of 0 to 5 C. but also at room temperature (up to 25 C.) and reversion took place at 37 C. These autoagglutinins with a thermal amplitude [6] of 0 to 25 C. were observed mostly under pathologic conditions, but some have been found in apparently normal and healthy persons. The number of reports has increased from year to year. The reader may be referred to the comprehensive papers of Rosenthal

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From the Pathologic Laboratories and the Department of Pediatrics, Jewish General Hospital.

1. Wiener, A. S.: Blood Groups and Transfusions, ed. 3, Springfield, Ill., Charles C Thomas, Publisher, 1943.

2. Reitman, A.: Ueber Bluterbrechen bei Leberzirrhose, Wien. klin. Wchnschr. **3**:423, 1890.

3. Klein, A.: Beiträge zur Kenntnis der Agglutination roter Blutkörperchen, Wien. klin. Wchnschr. **15**:413, 1902.

4. Ascoli, M.: Isoagglutinine und Isolysine, München. med. Wchnschr. **48**:1239, 1901.

5. Landsteiner, K.: Ueber Beziehungen zwischen dem Blutserum und den Körperzellen, München. med. Wchnschr. **50**:1812, 1903.

6. Thermal amplitude is the temperature range in which the activity of an antibody may be demonstrated.

and Korten,[7] Stats and Wasserman,[8] McCombs and McElroy[9] and others for a complete survey of the literature.

The indiscriminate use of different terms for the different types of this anomalous agglutinin has created much confusion. Some have called them panagglutinins and others cold agglutinins, using the expression for the agglutinins active at refrigerator as well as at room temperature. Even the agglutinins active at body temperature have been named "irregular cold agglutinins." It seems that the proper name for all three groups should be autoagglutinin, because that is the characteristic feature which distinguishes this type of agglutinin from all the other isoagglutinins as well as heteroagglutinins.

Most authors have stressed the fact that no autoagglutination occurs at 37 C. and that autoagglutination obtained at a lower temperature can be reversed by warming the serum-cell mixture to 37 C. Only within the past few years have a few observations been reported in which autoagglutination took place at body temperature. A search of the literature revealed the following cases, which may be described briefly. Only cases in which the reported tests give clear evidence of true autoagglutination occurring at 37 C., are included.

Ham and Castle[10] found such autoagglutinins in a 35 year old man suffering from acute hemolytic anemia and syphilis. The titer of the agglutinins was 1 to 1,025 at 5 C., 1 to 4 at 20 C. and 1 to 1 at 37 C. This patient received three transfusions without untoward effect and recovered. The autoagglutinin became gradually weaker.

Wiener[11] reported the case of a 16 month old child with staphylococcic sepsis and hemolytic anemia. The child had a severe reaction following the transfusion of incompatible blood (the blood was grouped wrongly because of autoagglutinins). The titer of the autoagglutinins was 1 to 64 at all three temperatures. This patient died.

Kracke and Hoffman[12] described the case of a 32 year old woman with chronic hemolytic anemia. No exact titration of the autoagglutinins is reported; the concentrated serum gave a reaction of almost equal strength at all three temperatures. The patient was given transfusions several times in the course of the disease. Some of the transfusions were followed by severe reactions; others were taken without any disturbances. A Wassermann test of the blood gave a positive reaction. The disease ended fatally.

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7. Rosenthal, F., and Korten, M.: Ueber das Phaenomen der Autoagglutination und über die Eigenschaften der Kälte-Hämagglutinine, Folia haemat. **58**:64, 1937.

8. Stats, D., and Wasserman, L. R.: Cold Hemagglutination: An Interpretive Review, Medicine **22**:363, 1943.

9. McCombs, R. P., and McElroy, J. S.: Reversible Autohemagglutination with Peripheral Vascular Symptoms, Arch. Int. Med. **59**:107 (Jan.) 1937.

10. Ham, T. H., and Castle, W. B.: Relation of Increased Hypotonic Fragility and of Erythrostasis to the Mechanism of Hemolysis in Certain Anemias, Tr. A. Am. Physicians **55**:127, 1940. Castle, W. B.: Personal communication to the authors.

11. Wiener, A. S.: Hemolytic Transfusion Reactions, Am. J. Clin. Path. **12**:189, 1942.

12. Kracke, R. R., and Hoffman, B. J.: Chronic Hemolytic Anemia with Autoagglutination and Hyperglobulinemia: Report of a Fatal Case, Ann. Int. Med. **19**:673 (Oct.) 1943.

Another case of hemolytic anemia with autoagglutination at 37 C. was reported by Evans.[13] The patient, a woman 32 years of age, received eighteen transfusions; those at the beginning were without reaction; later chills and asthmatic attacks became frequent. Since the transfusions were without effect, splenectomy was performed. In spite of further transfusions the patient died on the twentieth postoperative day. The autoagglutinins persisted after operation. The Wassermann reaction of the blood in this case was negative.

The case reported by Reisner and Kalkstein[14] may be added to this group, although there were no direct experiments at 37 C. However, the agglutination completed at room temperature persisted despite warming of the serum-cell mixture to 37 C., and the agglutinins could not be separated from the cells at this temperature. As will be shown later, the same is true of autoagglutinins active at 37 C. The case deals with a 43 year old man suffering from acute hemolytic anemia. Besides the autoagglutinin already mentioned, an atypical anti-O and anti-A_3 agglutinin was found in the serum. Six transfusions were all followed by severe reactions and were of no effect. After splenectomy two transfusions were tolerated, with a rise in the blood count despite the persistence of the autoagglutinins. The patient died, probably from hemorrhage in the gastrointestinal tract.

We were given the opportunity of making extensive studies of an autoagglutinin in the blood of an 11 year old boy who died of acute hemolytic anemia. The agglutinin was active at refrigerator, room and incubator temperature. Since such autoagglutinins are extremely rare and not yet investigated thoroughly, a publication of the case seems justified.

REPORT OF A CASE

History.—B. L. a boy aged 11½ years, was admitted to the pediatric department of the Jewish General Hospital Oct. 22, 1942. The complaints were a cough lasting for a month prior to admission, pallor for two weeks, a yellow tinge of the skin for one week and fatigue. Irregularly, for the past five years he had had frequent bleeding from the gums. Except for this bleeding, he had been in his normal good health until one month prior to this admission. He had had a slight "head cold" without fever or the necessity of taking to his bed but following this a slight cough developed which persisted up to the time of his admission but was apparently improving. The cough had never been productive; nor was it at any time accompanied with hemoptysis.

His mother had observed progressive pallor beginning two weeks before admission, while the yellow cast of his skin became evident one week before and did not increase in intensity. No changes were noted in the color of the urine or of the stools. Prior to the onset of the complaints for which he was admitted, he had been an apparently normal and active boy. A week before admission, however, he became somewhat lethargic and preferred to remain in bed.

For about four years before his last illness the mother noticed that his gums bled slightly whenever his teeth were brushed, but only on one occasion did he have a small hemorrhage from the gums. There was never any other bleeding; nor was any unusual tendency to bruising ever noted.

The family history was essentially irrelevant.

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13. Evans, R. S.: Acute Hemolytic Anemia with Autoagglutination, Stanford M. Bull. **1**:178, 1943.

14. Reisner, E. H., and Kalkstein, M.: Auto-Hemolysinic Anemia with Autoagglutination: Improvement After Splenectomy, Am. J. M. Sc. **203**:313, 1942.

Except for the removal of tonsils and adenoids at the age of 7 years and the usual mild attacks of the infectious diseases, scarlet fever at 6 years, measles and mumps at 8 years, whooping cough at 9 years and chickenpox at 10, there were no serious illnesses. Prior to the tonsillectomy he had been somewhat more prone to infections of the upper respiratory tract than since.

Clinical Examination.—As seen on admission, he was a tall, thin, yellow, apathetic boy, who weighed 75 pounds (34 Kg.). The rectal temperature was 100 F., the pulse rate was 90 per minute, and the respiratory rate was 22. The blood pressure was not unduly elevated, 118 mm. systolic and 80 mm. diastolic. He did not appear in any acute distress. The striking features of his appearance were the lemon yellow color of his skin and his extreme pallor. The heart was not enlarged to percussion, but on auscultation there was a loud systolic murmur well heard over the entire precordium but not transmitted beyond the cardiac borders. A few petechiae were present on the extremities and the trunk—about thirty in all—and a few ecchymoses on the arms and neck. The liver was not palpable, and the tip of the spleen could be felt just below the costal margin.

Preliminary Diagnosis.—The diagnostic impression at this time was that the disease was either acute leukemia or acute hemolytic anemia.

Hematologic Studies.—A hemogram made shortly after admission showed the following results: hemoglobin content, 4.05 Gm. per hundred cubic centimeters; color index, 1; red cells, 1,390,000, and white cells, 12,400 per cubic millimeter with the differential count showing meta myelocytes, 1 per cent; stab forms, 19 per cent; polymorphonuclear leukocytes, 55 per cent; eosinophils, 4 per cent; basophils, 1 per cent; lymphocytes, 14 per cent, and monocytes, 6 per cent. Thrombocytes numbered 120,000 per cubic millimeter, and the bleeding time was eight minutes. Coagulation began at five minutes and was completed at thirteen minutes. The prothrombin time was twenty-five seconds. Clot retraction was present. The blood serum had an icteric tinge. The result of the van den Bergh direct test was 0.86 mg. per hundred cubic centimeters; that of the indirect test was 3.63 mg. per hundred cubic centimeters, and the ratio was 23.7.

The conclusion of the hematologist, Dr. R. Gottlieb, was as follows: There is a pronounced degree of normochromic and macrocytic anemia. The hemogram is that of hemolytic anemia. There is no evidence of leukemia.

The reaction to the Wassermann test of the blood was 4 plus and to the Kline test 3 plus.

Urinalysis.—Examination of the urine showed the presence of urobilin but no other abnormalities.

Course.—The boy remained in the hospital for thirteen days. During this time the rectal temperature varied between 99.2 and 103.2 F. He was given seven transfusions without event but without benefit. The red cell count never rose above 1,840,000 per cubic millimeter, and the hemoglobin content remained correspondingly low. There was some blood regeneration as was evidenced by the fairly constant presence of approximately 25 per cent of the red cells as reticulocytes.

Despite all efforts, the boy showed no signs of rallying. The icterus gradually became deeper. The child slowly became comatose, and he died November 2. Postmortem examination was not permitted.

Serologic Studies.—In contrast to many of the reported cases, no difficulties were encountered in grouping the patient's red cells, which belonged to group A. This may have been due to the fact that the red cell suspension for grouping was made by placing a few drops of capillary blood directly into a test tube

containing isotonic solution of sodium chloride. Because of this procedure the autoagglutinins had no time and were too dilute to react with the red cells. When, however, the patient's serum was cross matched for transfusion with red cells of the same group, agglutination was observed after the mixture had been kept on a glass slide at 37 C. for half an hour. Further investigation concerning the nature of this abnormal agglutinin was initiated at once and revealed that the patient's serum agglutinated all groups of human red cells, including his own. The agglutinin was therefore regarded as an autoagglutinin effective not only at room temperature but also at body temperature.

To ascertain that the agglutination really occurred at 37 C., the following precautions were taken. Prepared serum dilutions (0.2 cc.), thrice washed red cell suspensions and the necessary glassware were kept at each of the three essential temperatures, namely, in the incubator, at room temperature and in the refrigerator, for one hour in order to bring everything to the same temperature as that in which the tests were to be made. Then 1 drop of the serum dilutions and 1 drop of red cell suspension were transferred to a glass slide and mixed with a toothpick; for a second test 0.1 cc. of the cell suspension was transferred into each of the serum dilutions. The mixing was done inside the incubator or the refrigerator, respectively. The slide tests were kept for one hour and the tube tests for two hours at the different temperatures, before reading. Agglutination was found to a titer of 1 to 4 with the patient's own red cells as well as with another strain of A and a strain of O cells at all three temperatures tested.

Absorption tests were carried out to confirm the results of direct agglutination. One cubic centimeter of the patient's serum was placed in each of six small test tubes. To the contents of three tubes 0.5 cc. of concentrated thrice washed A cells was added, and O cells were added to the remaining three tubes. Two tubes (one with A and one with O cells) were then kept for one hour in the refrigerator, two tubes were kept at room temperature and two in the incubator. All were then centrifuged, during which procedure the tubes were kept at the respective temperatures by packing them in cracked ice or warm water respectively. The supernatant serum was then withdrawn, and each of the six absorbed serums was mixed with A or B or O cells and kept at the three different temperatures. The tests were performed on slides. No agglutination occurred with A or O cells at any temperature with any of the absorbed serums, whereas the B cells were as strongly agglutinated as in the unabsorbed control. Therefore, the autoagglutinin was absorbed at all temperatures, which suggests that the agglutinins active at the different temperatures are the same.

Further experiments were done with purified agglutinins. For this a technic which differed slightly from the one described by Landsteiner [5] was used. Undiluted serum (0.5 cc.) was mixed with 0.1 cc. of thrice washed packed red cells of group A. One tube was kept in the refrigerator and another in the incubator. All the materials used were kept at the respective temperatures for one hour prior to the mixing. The mixtures were allowed to stand for three hours and were then centrifuged in cups containing cracked ice or warm water. The serum was then removed, and the sedimented cells were washed twice with ice cold or with warm isotonic solution of sodium chloride, respectively. The cells were resuspended in 0.5 cc. of isotonic solution of sodium chloride, kept in a water bath at 56 C. for five minutes under gentle shaking and then centrifuged in a cup containing warm water (56 C.). The supernatant slightly pinkish fluid was withdrawn and tested against several strains of A and O cells as well as against animal cells (cells of the patient could not be used, since he had died in the mean-

time). Because of the small amount of material available, the slide method only was used; one series of slides was kept in the refrigerator and another in the incubator.

The results of all four series were practically identical, differing only in the intensity of the clumping. For this reason only one series is reported in the table.

Agglutination of Different Red Cells by Purified Agglutinins

Type of Red Cells		Type of Red Cells	
Group A	+	Sheep	+
Group O	+	Beef	—
Rabbit	+	Goose	—
Duckling	±	Chicken	—

Therefore, the purified agglutinins extracted at refrigerator temperature as well as at incubator temperatures were active not only against all groups of human cells but against some animal red cells.

Tests for autohemolysins were negative with whole blood as well as with purified agglutinin.

A few experiments to test the inhibiting influence of saliva on the autoagglutination yielded negative results. Unfortunately, saliva from the patient himself was not tested.

From all these experiments it appears that the autoagglutination at 37 C. is principally the same phenomenon with the same characteristics of the antibodies as described by Landsteiner for the autoagglutination at refrigerator temperature and by others for the autoagglutination at room temperature.

COMMENTS

Autoagglutination active at refrigerator temperature and with a low titer not exceeding 1:20 has been found so often in normal persons that it is regarded as a normal physiologic phenomenon. However, when an increase in the titer of the agglutinins at this temperature or an increase in the thermal amplitude has been found, it has almost always been under pathologic conditions. An increase in the titer at refrigerator temperature has recently been reported to occur in so-called atypical pneumonia of unknown origin (virus pneumonia).[15] Unfortunately, the authors who reported it did not perform tests at higher temperatures. Others[16] found in connection with the same disease an increase in the thermal amplitude. They did not perform tests in the refrigerator. It may be that both phenomena, the increase in titer at 0 to 5 C., as well as the increase in the thermal amplitude, go together in this disease. This assumption is partly confirmed by Heiklejohn,[17] who found that positive autoagglutination tests with a very high titer at 0 to 5 C. were active at room temperature also (up to 21 C.).

15. Turner, J. C.; Nisnewitz, S.; Jackson, E. B., and Berney, R.: Relation of Cold Agglutinins to Atypical Pneumonia, Lancet **1**:765, 1943. Petersen, O. L.; Ham, T. H., and Finland, M.: Cold Agglutinins (Autohemagglutinins) in Primary Atypical Pneumonias, Science **97**:167, 1943. Horstmann, D. M., and Tatlock, H.: Cold Agglutinins, J. A. M. A. **122**:369 (June 5) 1943.

16. Shone, S., and Passmore, R.: Pneumonitis Associated with Autohemagglutination, Lancet **2**:445, 1943.

17. Heiklejohn, G.: The Cold Agglutination Test in the Diagnosis of Primary Atypical Pneumonia, Proc. Soc. Exper. Biol. & Med. **54**:181, 1943.

Other diseases which have been reported in connection with autoagglutination at room temperature should be mentioned as follows: hemolytic anemia, hemolytic anemia following therapy with sulfonamide compounds, hemolytic icterus, paroxysmal hemoglobinuria, trypanosomiasis, malaria, kala azar, chronic sepsis and benzene poisoning. The same kind of autoagglutinins have also been found in a small number of apparently healthy persons.[18]

Autoagglutinins active at 37 C. have all been found hitherto in connection with hemolytic anemia only (6 published cases). It was the only diagnosis in 4 cases; twice there were accompanying diseases (staphylococcic sepsis and latent syphilis). Five cases were reported with fatal terminations after shorter or longer illness; in 3 a positive reaction to a Wassermann test was reported.

The titer of the autoagglutinins at 37 C. varied from undiluted to 1 to 64. In 3 cases the titer was the same at the different temperatures; in 1 case it decreased from 1:1025 at refrigerator temperature to 1:4 at room temperature and 1:1 at 37 C.

Little is known with certainty concerning the origin of autoagglutinins. In the opinion of Wiener they are the result of autoimmunization due to a massive destruction of red cells. The reticuloendothelial system, which normally takes care of destroyed red cells, is unable to handle the increased amount, which becomes antigenic. However, this theory, plausible as it may seem, especially in the case of hemolytic anemia, fails to explain why these agglutinins are found in diseases without massive destruction of red cells and even in normal healthy persons; why they are found only in a small percentage of cases of hemolytic anemia, and why they are so nonspecific as to act on almost any kind of red cells.

The occurrence of autoagglutinins in diseases in which massive destruction of red cells is not a constant feature suggests some other substance as an agent in the production of the autoantibodies. One may think of one or several more or less closely related antigens, heterogenetic in character, which may be present in certain protozoa, toxic agents and viruses. However, the striking fact, that autoagglutinins at the higher temperatures have been found frequently connected with positive reactions to Wassermann and flocculation tests, suggests that both phenomena may be related to each other and that the same cause may be responsible for their appearance. Since many of the reported cases as well as that of our own patient did not present clinical evidence or history of syphilis and the serologic reactions became negative after recovery, these reactions may be regarded as nonspecific. A relationship between autoagglutination and the Wassermann reaction is furthermore suggested by the following observations. York[19] succeeded in producing autoagglutinins in lower animals by infecting them with trypanosomes, whereas Landsteiner and van der Scheer[20] have shown that serums of rabbits immunized with killed trypanosomes gave a positive reaction to the Wassermann test. Sachs and his co-workers[21] could achieve the same

18. Shooter, R. A.: Preparation of Grouping Serum, Lancet **1**:202, 1943. Rosenthal and Korten.[7]

19. York, W.: Autoagglutination of Red Blood Cells in Trypanosomiasis, Ann. Trop. Med. **4**:529, 1910.

20. Landsteiner, K., and van der Scheer, J.: Experiments on the Production of Wassermann Reagins by Means of Trypanosomes, J. Exper. Med. **45**:465, 1927.

21. Sachs, H.; Klopstock, A., and Weil, A.: Die Entstehung der syphilitischen Blutveränderung, Deutsche med. Wchnschr. **51**:589, 1925. Sachs, H.: Zur Theorie und Methodik des serologischen Luesnachweises, Klin. Wchnschr. **4**:1630, 1925.

reaction with the serum of rabbits which had had injections of lipids and of pig serum or of alcoholic extracts of normal organs mixed with pig serum. They concluded that the antigens for the Wassermann reaction are composed of lipid-proteins of the spirochetes or of tissue lipids combined with proteins of spirochetes or of lipids of spirochetes plus tissue proteins or even of lipids and proteins of tissue destroyed by the disease.

In a similar way the antigen for autoagglutinins may be composed (1) of a substance derived from protozoa or virus or toxic agents, whatever may be the cause of the disease, and (2) of some part of the red cells, one delivering the lipid and the other the protein. The combination may alter the red cell or part of it in such a manner that it may act as an antigen in and against its own serum.

Closely connected with the question of origin is the question of the pathognomonic significance of these autoantibodies. Many authors are inclined to attribute at least a secondary role to the autoagglutinins in the destruction of red cells during the course of acute hemolytic anemia. As Wiener [1] said: "Autoagglutination may be the result rather than the primary cause of the disease (acute hemolytic anemia). Once they [autoagglutinins] appear, they may aggravate the symptoms and a vicious circle may be established." However, in the vast majority of cases not only the autoagglutinins are inactive at body temperature, but the reaction after completion at a lower temperature is reversible at 37 C. According to the unitarian view, agglutinins and hemolysins are the same antibody acting differently under different conditions, agglutination occurring mostly in the test tube and hemolysis occurring in vitro and in vivo. It is not yet proved experimentally that a hemagglutinin not acting at body temperature can act as a hemolysin at this temperature, and the presence of true autohemolysins has not been demonstrated definitely. In most cases no hemolytic effect could be achieved in the test tube with the patient's serum. In a few cases in which a hemolytic effect has been reported, it is doubtful whether this effect was due to an autohemolysin. Furthermore, in many cases the presence of autoagglutinins was not connected with a hemolytic phenomenon, and in some cases the agglutination remained demonstrable after the hemolytic anemia had disappeared.

Others have described autoagglutination as occurring in the human body itself. Stats and Bullowa [22] could see a decided segmentation of red cells—apparently by clumps of erythrocytes—in the capillaries of the conjunctiva after the conjunctival sac was irrigated with ice-cold isotonic solution of sodium chloride for one and one-half minutes. The patient had an extremely potent autoagglutinin in his serum (titer 1:3,200), and agglutination in the test tube was completed within two minutes after the cooling had started. This described procedure, however, created conditions which do not occur naturally.

McNeil [23] found, in a fatal case of atypical pneumonia with a high titer of cold agglutinins, a pathologic picture which was strikingly similar to multiple pulmonary infarction. He expressed the opinion that small groups of agglutinated red cells could form in a relatively cold extremity and act as multiple emboli. It is difficult to understand how an extremity of a patient resting in bed for ten days with fever could cool sufficiently to allow an agglutination. It seems rather reasonable to assume that this was a postmortem phenomenon. All

22. Stats, D., and Bullowa, J. G. M.: Cold Hemagglutination with Symmetric Gangrene of the Tips of the Extremities, Arch. Int. Med. **72**:506 (Oct.) 1943.

23. McNeil, C.: The Relationship of Cold Agglutinins to the Course of Primary Atypical Pneumonia, Am. J. M. Sc. **209**:48, 1945.

postmortem observations of agglutinated red cells in cases connected with the presence of autoagglutinins during life should be evaluated cautiously.

In the opinion of Damashek,[24] the renal shutdown in some cases of acute hemolytic anemia is probably due to agglutination of the red cells within the glomeruli and subsequent blockage of renal tubules, as in the case of reactions to transfusion of incompatible blood. But it is now generally believed that the renal symptoms in such transfusion accidents are caused by the hemoglobin released from the incompatible broken-down erythrocytes. The blocking of the tubules is assumed to be caused by acid hematin.

There is no conclusive proof that autoagglutinins are formed spontaneously by the human body and that they can be the primary cause of hemolytic diseases. Only when autoagglutinins are active at body temperature can it be logically assumed that they could play a secondary role, but this too is far from proved. It must be kept in mind that in cases in which autoagglutinins are connected with a hemolytic phenomenon there is always something else which is primarily responsible for the hemolysis in vivo.

Therefore, autoagglutination may be a test tube reaction only, with no pathognomonic importance; perhaps it is similar to the Weil-Felix reaction and the Paul Bonnel test.

The importance of the autoagglutinins lies in the fact that they are a source of error in blood grouping. It may be that they can be used as diagnostic aids in certain diseases like atypical pneumonia, but even this is not yet definitely established.

SUMMARY

1. Autoagglutination occurring at the three temperatures (0 to 5 C., 25 C. and 37 C.) is caused by the same antibody as shown by absorption tests and experiments with purified agglutinins.

2. Autoagglutination is probably a test tube phenomenon only of no pathognomonic importance.

3. Autoagglutinins may be produced by the same factors which cause the (false) positive Wassermann reaction in many of the reported cases.

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24. Damashek, W.: Cold Hemagglutinins in Acute Hemolytic Reactions, J. A. M. A. **123**:77 (Sept. 11) 1943.

TREATMENT OF CRYPTOCOCCIC MENINGITIS WITH PENICILLIN

Report of a Case

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UP TO the present time 97 cases of meningitis due to Cryptococcus have been reported. More than one complete review of the literature has been published, with an analysis of cases. We wish to add 1 case, in which we had the opportunity to study the effects of penicillin on the organism in vivo. The case was that of a child of 6 years, in an age group in which the disease is exceedingly rare, but the manifestations and the course were typical. The effects of penicillin were closely followed culturally, and correlation of penicillin levels and cultural results was attempted. As in the majority of cases, the diagnosis in this one was made late; the disease is notorious for its ambiguity and for difficulty of clinical recognition. The cultural results in this case were promising and are reported here in the hope that with earlier diagnosis, therapy with penicillin may result in improving the prognosis of this generally hopeless condition.

Cryptococcus neoformans is more familiarly known as Torula histolytica; other synonyms include Cryptococcus hominis and Blastomycoides histolytica. There are many strains of varying virulence, and the disease shows many degrees of severity and duration. The organism has definite characteristics as revealed by smear, culture and animal inoculation, which are adequately described elsewhere, and the diagnosis is easily made when suspected. We feel that the disease should be suspected in all cases of acute or chronic meningitis when satisfactory proof of other cause is not at once apparent. Early diagnosis will undoubtedly improve clinical results, especially if further study confirms these encouraging in vivo results with penicillin.

Only 2 previous cases of proved cryptococcic meningitis were found in the records of Charity Hospital for the past ten years. One, that of a 25 year old white man, was encountered in 1943, but the disease was not diagnosed at that time. Follow-up correspondence about his case revealed that the diagnosis of torula meningitis was made elsewhere

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about five months after the onset of his illness; he was treated with one intrathecal injection of tyrocidin together with oral administration of sulfathiazole. The patient continued to take sulfathiazole, and he still (August 1945) has symptoms to suggest a persistence of the infection. The disease occurred in a second case during 1943, in a Negro man of 52 years. The diagnosis was made three months after the onset, and treatment with sulfadiazine and iodides was of no avail. This case is to be reported elsewhere. A fourth case, that of a Negro man, is now being studied by the medical service of this hospital, with a diagnosis of cryptococcic pneumonitis. These cases are men-

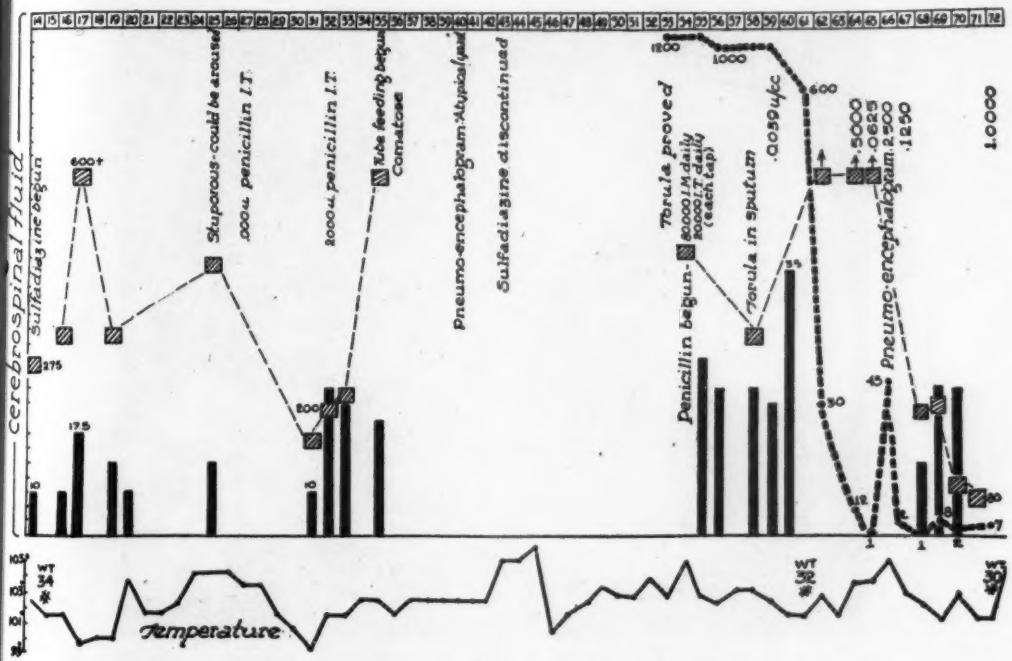

Fig. 1.—Clinical course of patient E. M., a boy aged 6 years, with torular meningitis, showing the effect of the administration of penicillin intrathecally. (Days of illness are recorded above; cerebrospinal fluid pressure is indicated by blocks joined by dashes; cerebrospinal fluid sugar is indicated by heavy bars; number of organisms per cubic centimeter is indicated by a heavy dotted line. Vertical numbers refer to penicillin levels in the cerebrospinal fluid.)

tioned to indicate that the disease may be more prevalent than the small number of recorded cases would indicate.

REPORT OF CASE

E. M., a 6 year old Negro boy, was admitted on April 14, 1945, complaining chiefly of headache and vomiting. He had been sick for only two weeks, with malaise, anorexia and occasional vomiting. Headache and fever were noted one week before admission, and he "vomited everything." A generalized convulsion

occurred just before he was brought to the hospital. Past and family histories seemed noncontributory.

Physical examination revealed a Negro boy weighing 34 pounds (15.4 Kg.); his temperature was 102.4 F., the pulse rate 130 per minute and the respiratory rate 33 per minute. He was acutely ill and extremely irritable. Other abnormal conditions included a coated tongue, an injected pharynx and cervical lymphadenopathy; the neurologic examination showed pronounced nuchal rigidity, bilateral moderate papilledema, positive Brudzinski and Kernig signs and normal reflexes except for absence of knee jerks.

The hemoglobin content was 83 per cent (Sahli); the leukocyte count was 13,120 per cubic millimeter with 52 per cent neutrophils, 32 per cent immature cells and 16 per cent lymphocytes. Results of tests for sickle cells and reactions

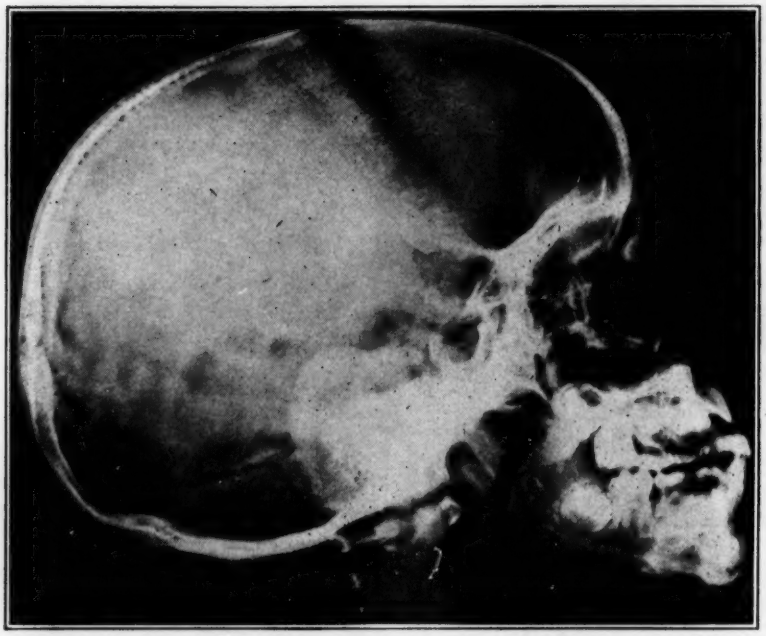

Fig. 2.—Lateral view of pneumoencephalogram (E. M., May 10, 1945), showing evidences of increased intracranial pressure.

to serologic tests for syphilis were negative. A routine urinalysis revealed nothing abnormal, and Schick and Mantoux tests elicited negative reactions (the latter with amounts up to 1.0 mg. of old tuberculin). A culture from the throat yielded beta hemolytic streptococci.

The survey at the time of admission showed that the spinal fluid was under a pressure of 335 mm. of water, was clear in appearance and had 320 cells per cubic millimeter, of which 50 per cent were thought to be red cells, 30 per cent lymphocytes and 20 per cent polymorphonuclear leukocytes. The total protein was 180 mg., the dextrose less than 10 mg. and the chlorides 666 mg. per hundred cubic centimeters. Results of routine bacteriologic cultures, the Kline and Kolmer tests and the colloidal gold test were reported as negative. A roentgenogram of the chest revealed only scattered infiltration suggestive of a nonspecific infection

of the upper respiratory tract. Further pertinent studies of the spinal fluid are presented in the chart (fig. 1). Three specimens were found negative for tubercle bacilli. Other significant laboratory data follow.

Hydration was accomplished by the usual means, and the administration of sulfadiazine was begun at the time of admission on a dosage scale of 2 grains per pound of body weight (0.25 Gm. per kilogram) every twenty-four hours; this was continued for one month. The patient complained more and more of headache in spite of frequent decompression by withdrawal of spinal fluid, and opisthotonos increased. Eleven days after admission, on April 25, he became stuporous, and he never regained consciousness. The temperature was septic in type, spiking between 100 and 106 F. during the entire course. The patient was nourished through a

Fig. 3.—Anteroposterior view of ventriculogram, showing dilatation of both ventricles (E. M., June 2).

gastric tube, and supportive transfusions and intravenously administered fluids were given at close intervals. On April 27, 20,000 units of penicillin was given intrathecally on an empiric basis, and a remission of temperature ensued. This was repeated four days later with no apparent benefit. Since the supply of penicillin was limited, no more was administered. Tuberculous meningitis was considered the most likely diagnosis.

The Francis test, with the use of polysaccharides of Hemophilus influenzae, was performed on April 27 because it was felt that the patient might possibly have had unrecognized influenzal meningitis, with the formation of a basilar abscess. The results of this test could not be properly evaluated.

In view of the possibility of basilar meningitis, with adhesions and encapsulation preventing the recovery of causative organisms or making them inaccessible to therapy, a pneumoencephalogram was done on May 10 in an effort to break down mechanically any such obstruction and allow more effective therapy. Roentgenograms at this time showed pronounced enlargement of one ventricle; the other was not visualized (fig. 2).

Fliud withdrawn by cisternal puncture on the fortieth day of illness produced a yeast of uncertain identity; however, this resembled C. neoformans to such

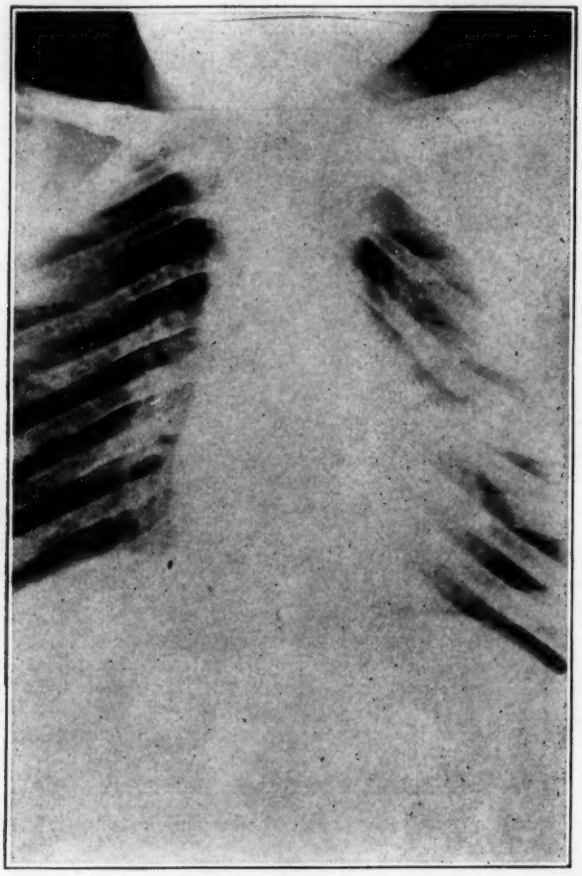

Fig. 4.—Roentgenogram of chest, showing pneumonic infiltration probably due to C. neoformans (E. M., June 9, 1945).

a degree that its pathogenicity was determined by inoculation of mice. The test animals died, and the pathogen was observed in various organs. Culture materials were also positive for the pathogen. On May 23, an examination of the spinal fluid directly identified the organism as C. neoformans, and therapy with penicillin was begun. Ten thousand units was injected intramuscularly every three hours, and 20,000 units, in a dilution of 1,000 units per cubic centimeter, was injected intrathecally after each tap. This treatment was repeated daily except for four of eighteen days, and frequent simultaneous cisternal and lumbar taps

were done to determine the presence and/or prevent the formation of blocks in the spinal canal. On June 2, with no clinical improvement, because one ventricle had not been visualized in the earlier pneumoencephalogram, ventriculography was performed through a catheter placed in the ventricle after trephination. Roentgenograms now showed both ventricles to be greatly dilated. Penicillin was subsequently given directly into the ventricle (fig. 3).

The fact that a specimen of sputum was found to contain C. neoformans indicated that the pneumonic process seen by roentgenogram was probably due to this organism (fig. 4).

The action of penicillin on C. neoformans was observed by culturing spinal fluid at intervals of one to two days during treatment. The technic employed gave a crude quantitative measure of the number of viable fungi per cubic centimeter of spinal fluid. In this procedure the freshly drawn specimens of spinal fluid, ranging from 4 to 7 cc., were centrifuged at low speed for three minutes, and the organisms were carefully collected from the centrifugate by aspirating 0.5 cc. of the sediment with a Kahn pipet. This material was added to 10 cc. of liquid Sabouraud agar (at approximately 45 C.); the resulting mixture was then poured into Petri dishes. The cultures were incubated for seven days at room temperature, and the number of organisms per cubic centimeter of spinal fluid was calculated on the basis of volume of specimens.

Results of a Study of the Action of Penicillin on C. Neoformans

Date	Source of Fluid	Colonies of C. Neoformans/Cc.	Penicillin (Oxford Units/Cc.)
5/23/45	Lumbar	1,200	
5/25	Lumbar	1,200	
5/26	Lumbar	1,000	
5/28	Lumbar	1,000	
5/29	Cisternal	1,000	0.0039
5/31	Lumbar	600 *	0.0156
6/ 1	Lumbar	30 *	0.0156
6/ 3	Ventricular	12 *	0.5
6/ 4	Lumbar	1 *	0.0625
6/ 5	Cisternal	2 *	0.0156
6/ 5	Cisternal	5 *	
6/ 6	Lumbar	45 *	0.125
6/ 7	Cisternal	1 *	
6/ 8	Lumbar	8 *	
6/ 9	Lumbar	2 *	
6/11	Cisternal	7 *	1

* Approximately.

The results of this study (table) revealed that penicillin caused a precipitous decline in the number of fungi. Prior to the administration of the drug and during the first six days after treatment was initiated, there were over 1,000 organisms per cubic centimeter of spinal fluid. However, between the seventh and tenth days of treatment the number decreased sharply, and it remained low after the ninth day. Although penicillin therapy extended over a period of eighteen days, the spinal fluid was never completely cleared of the parasite (table).

The effect of penicillin was so remarkable that there seems to be no doubt as to the general interpretation of these results. However, it is also obvious that the procedures used do not permit an exact quantitative determination of the effects of this agent. The greatest error probably occurred in the method of concentrating and removing organisms from the spinal fluid. An attempt was

made to standardize these manipulations by performing them in the same manner each time, with special care to aspirate only the sediment from the bottom of the centrifuged specimens. The general procedures in this study had the advantages of determining the approximate number of viable organisms and of minimizing the in vitro effects of residual penicillin in the specimens of spinal fluid. These effects could not have been accomplished by a direct microscopic count of the fungi. Furthermore, if cultural methods were to be employed, it was desirable to dilute the residual spinal fluid penicillin, since Hobby and his associates [1] have found that C. neoformans is extremely sensitive to penicillin in vitro.

The antifungal action of penicillin in vivo as indicated by the cultural studies was corroborated by the microscopic examination of the centrifuged spinal fluid. Prior to the administration of penicillin several organisms occurred in each high power field, but after treatment had been continued for nine days it was difficult or impossible to demonstrate the presence of the organisms microscopically.

Simultaneously with cultural studies to determine the number of viable fungi, penicillin assays were made on 7 specimens of spinal fluid. Results (table) indicate that the drug did not reduce the number of fungi until the penicillin level, determined twenty-four hours after previous intrathecal injection, had reached a concentration greater than 0.0156 unit per cubic centimeter. The penicillin assays were made by the method of Rammelkamp and co-workers [2] with Bacillus subtilis as the test organism.

In vitro studies of the effects of penicillin on the strain of C. neoformans from this patient revealed that it was sensitive to the drug. These observations, using the methods of Rammelkamp and associates,[2] corroborate the in vitro findings of Hobby and associates.[1]

Complement-fixing antibodies were not demonstrable in the serum of this patient. These studies were repeated three times with the same specimen of serum, taken the day before death. The tests were performed according to the procedures outlined by Conant and his associates.[3]

In spite of the dramatic fall in the number of organisms which could be cultured from the spinal fluid, the patient showed no clinical improvement. The spinal fluid sugar, as shown in the chart (fig. 1), did exhibit a definite rise, though it never became normal, both after the empiric therapy with penicillin and after the more intensive later course was started. The pressure of the fluid dropped somewhat but promptly rose again. The rise after the intensive penicillin therapy was perhaps due partly to the operation of trephination (fig. 1).

COMMENT

This patient is the third under 10 years of age for whom a diagnosis of cryptococcic meningitis has been reported. The diagnosis, as in so many cases, was made late, and at a time when irreparable damage to the brain undoubtedly had already occurred. The administration of

1. Hobby, G. L.; Meyer, K., and Chaffee, E.: Activity of Penicillin in Vitro, Proc. Soc. Exper. Biol. & Med. **50**:227 (June) 1942.

2. Rammelkamp, C. H.: A Method for Determining the Concentration of Penicillin in Body Fluids and Exudates, Proc. Soc. Exper. Biol. & Med. **51**:95 (Oct.) 1942.

3. Conant, N. F.; Martin, D. S.; Smith, D. T.; Baker, R. D., and Callaway, J. L.: Manual of Clinical Mycology, Philadelphia, W. B. Saunders Company, 1944, pp. 121-122.

sulfadiazine in adequate dosage had no discernible effect on the course of the disease, as evidenced by the lack of clinical improvement and the extremely large numbers of organisms that were demonstrated. Penicillin was used because in vitro sensitivity of the organism had been demonstrated by Hobby and co-workers.[1] One hundred thousand units was given daily, or approximately 6,700 units per kilogram every twenty-four hours. This was continued for eighteen days, with a total administration of 1,740,000 units. Culturally, improvement was noted within eight days. Perhaps even higher dosage should have been used. Little or no clinical improvement occurred, but even if cultural sterility had been obtained immediately on beginning the administration of penicillin, it is extremely doubtful that the results would have been any better. Earlier diagnosis might have permitted a more favorable outcome.

To our knowledge, penicillin has never been used previously in the treatment of cryptococcic meningitis. All types of treatment have been generally unsatisfactory. Iodides have been used frequently both orally and intravenously. In Lynch's [4] and Reale's [5] cases, results were poor. In Toone's case,[6] apparent cure resulted, but symptoms recurred two years later, and the result of culture of the spinal fluid was positive. The patient was not acutely ill at that time but had signs of chronic meningeal irritation. On three separate occasions Warvi and Rawson [7] treated with roentgen rays a patient whose condition had been diagnosed as an example of Hodgkin's disease with cryptococcic meningitis. Remission occurred twice, but the patient died eighteen months after the onset of neurologic symptoms. Acriflavine has been used intrathecally [8] with no beneficial results. Goldberg [9] treated a patient whom he suspected of having tuberculous meningitis with massive doses of vitamin D and secured dramatic improvement; the disease recurred five months later, at which time a diagnosis of crpytococcic meningitis was made a few days before death.

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4. Lynch, F. B., Jr., and Rose, E.: Torula Meningitis, Ann. Clin. Med. **4**:756 (March) 1926.

5. Reale, E.: A Case of Meningitis Due to the Torula Histolytica, Morgagni **73**:66 (Jan. 11) 1931.

6. Toone, E. C.: Torula Histolytica (Blastomycoides Histolytica) Meningitis: Report of a Case with Recovery, Virginia M. Monthly **68**:405 (July) 1941.

7. Warvi, W. N., and Rawson, R. W.: Torula Meningitis, Arch. Int. Med. **69**:90 (Jan.) 1942.

8. Nichols, I. C.: Torula Meningoencephalitis: Report of a Case, Rhode Island M. J. **24**:221 (Dec.) 1941. Warvi and Rawson.[7]

9. Goldberg, L. H.: Torula Infection of the Central Nervous System: A Report of a Case with Necropsy Findings, J. Lab. & Clin. Med. **26**:299 (Nov.) 1940.

Sampson and Farren [10] employed sulfapyridine in 1 case. Death of the patient occurred one month after therapy was initiated and six months after onset. Reeves and his associates [11] reported the apparent cure of a patient treated empirically with azosulfamide at the onset. Eight months later these investigators saw the patient and made the diagnosis, at which time administration of potassium iodide was begun. Three courses of various sulfonamide compounds, each of seven to ten days' duration, and two injections of torula antigen were given. This patient still had symptoms of meningeal irritation but was improving three years after the onset. Marshall and Teed [12] reported an apparent cure (patient followed for five months) after a bilateral mastoidectomy and administration of sulfadiazine and potassium iodide.

Administration of sulfadiazine had no apparent effect on the course of the disease in the second case mentioned earlier in this paper. Sulfathiazole was used in the first case five months after onset of the disease; this patient is living but still has symptoms thirty-two months after onset.

To summarize, all forms of treatment used in this disease have failed more times than they have succeeded. Patients for whom therapy has been successful have usually been those with slow progress of the disease, in whom the causative strain of the organism was apparently of relatively low virulence. Penicillin has now been used for 1 patient, and we find no reports of others so treated. Clinical results were far from gratifying, but quantitative cultural results seem to suggest that penicillin may destroy C. neoformans in vivo. Further studies will be necessary to establish the most effective plan to maintain relatively high concentrations of penicillin in cerebrospinal fluid.

SUMMARY

Observations have been made concerning the effect of sodium penicillin in the treatment of meningitis due to C. neoformans.

Dr. G. von Langermann, of the Department of Clinical Pathology, Tulane University of Lousiana School of Medicine, assisted us by testing for complement-fixing antibodies.

10. Sampson, B. F., and Farren, J. E.: Another Case of Torula Meningitis, South African M. J. **16**:245 (July) 1942.

11. Reeves, D. L.; Butt, E. M., and Hammack, R. W.: Torula Infection of the Lungs and Central Nervous System: Report of Six Cases with Three Autopsies, Arch. Int. Med. **68**:57 (July) 1941.

12. Marshall, M., and Teed, R. W.: Torula Histolytica Meningoencephalitis, J. A. M. A. **120**:527 (Oct. 17) 1942.

Abstracts from Current Literature

Prematurity and Congenital Deformities

PRODUCTION OF ACIDOSIS IN PREMATURE INFANTS BY PROTEIN MILK. D. C. DARROW, M. MARTINS DA SILVA and S. S. STEVENSON, J. Pediat. **27**:43 (July) 1945.

Feeding with protein milk powder with or without added carbohydrate produces acidosis in premature infants. The acidosis is characterized by a low p_H, a low level of bicarbonate and usually a high level of chloride in the serum. The babies become pale and listless, lose their appetite and sometimes show Kussmaul breathing; the stools are not loose, nor does ketosis develop.

Balance studies show that the acidosis is due to excessive retention of chloride in relation to sodium. The relative excess of chloride is equivalent to about one third of that normally present in extracellular fluids. In this process, extracellular water increases, intracellular water decreases and weight is lost. Intracellular sodium is transferred to extracellular fluids in amounts equivalent to about all the sodium which is normally in the intracellular phase of muscle. In 1 case a deficit of phosphate and potassium developed, but in the other cases the retention of nitrogen, phosphorus, potassium and calcium was essentially normal.

The acidosis can be prevented by the addition of sodium bicarbonate to protein milk powder. Acidosis does not develop when the infant is on a diet of HI-PRO (a mixture of powdered whole milk and separated milk from which some lactose has been removed), a food of similar organic but different electrolyte composition. In the manufacture of protein milk powder about 2 millimols of calcium is added and 2 millimols of sodium is lost per hundred calories; this is sufficient to explain the development of acidosis.

It is pointed out that the poor renal function of premature infants explains their susceptibility to small changes in the intake of sodium and chloride. It is likely that this fact must be taken into account in other foods used for feeding premature and young infants.

The importance of transfer of intracellular sodium to extracellular fluids is discussed. The amount involved is equivalent to one ninth of total extracellular sodium or a large part of extracellular sodium bicarbonate. This quantity probably plays an important role in other types of acidosis and must be considered in estimating the deficit of body sodium in acidosis.

AUTHORS' SUMMARY.

A SPEECH TRAINING CENTER FOR CLEFT PALATE CHILDREN. CHARLOTTE G. WELLS, Quart. J. Speech **31**:69, 1945.

A description is given of the Wisconsin state project of the Bureau of Handicapped Children in setting up a training center in Madison, during the summers of 1943 and 1944 for the children of the state with cleft palates. The program has not met all the needs of children with cleft palates, but it is hoped that the results obtained from the experiment in short term intensive speech training will serve as a basis for further services, not only to children with cleft palates and cleft lips, but to children in Wisconsin with all types of speech handicaps.

PALMER, Wichita, Kan.

ON THE PATHOGENESIS OF RICKETS IN PREMATURE CHILDREN. GERT VON SYDOW, Nord. med. (Hygiea) **24**:2029 (Nov. 10) 1944.

Comparative feeding experiments under well controlled conditions with premature infants, especially pairs of premature twins, have confirmed the known fact

that when fed on breast milk alone, without vitamin D or with an insufficient addition of this vitamin, rickets may develop in these infants within a short time after birth. It has also been established, however, that when of fully comparable infants, e. g., twins, under otherwise identical conditions, one is fed on breast milk and the other on cow milk mixtures, the first acquires rickets while the second escapes the disease. Rickets in breast-fed premature infants may be brought to distinct healing solely by replacing breast milk with cow's milk. Corresponding experiments on full term infants have not given similar results. The author believes that the low mineral content of breast milk gives rise to an absolute mineral deficiency in the premature infants with their rapid growth and low milk consumption.

WALLGREN, Stockholm, Sweden.

Newborn

INCIDENCE OF THE BLOOD RH FACTOR IN THE CITY OF MEXICO. MENA BRITO and PÉREZ MICHAUD, Bol. méd. d. Hosp. inf., México **3**:159 (July) 1945.

The authors insist on the necessity of having a constant supply of Rh-negative blood in the blood bank of the Hospital del Niño.

A decription of Levine's technic for determining the Rh factor is given.

The statistics obtained at the authors' hospital from the study of all bloods are as follows: number of bloods studied, 1,500, Rh-positive, 1,425 (95 per cent); Rh-negative, 75 (5 per cent).

MADERO, México, D. F., Mexico.

ERYTHROBLASTOSIS NEONATORUM. MAIA BITTENCOURT, Rev. de ginec. y d'obst. **1**:23 (Dec.) 1942.

A complete report of a case of erythroblastosis neonatorum is presented. The maternal data are as follows: personal hereditary and pathologic antecedents, of no importance; vulvar and cervical edema before delivery; no engagement of the fetal head; cesarean operation, and dismissal of the patient from the hospital twenty-nine days later in good health.

The fetus was born dead, with a monster appearance, having hard edema of the whole body and attachment of the head to the thorax owing to the shortness of the neck. Serologic reactions were negative. Findings at autopsy were as follows: general congenital hydrops; hydroperitoneum; double hydrothorax; hyperemia of the spleen, liver, kidneys and lungs, and meningeal edema. The spleen and the bone marrow showed increased erythroblastosis.

Finally, the author makes an abstract of the etiologic and pathogenic ideas about the disease, noting the influence of the Rh factor.

LOZOYA, México, D. F., Mexico.

A TRANSITORY CHANGE OF THE JAW IN THE NEWBORN. KARL KAWALEK and ERICH NASSAU, Ann. pædiat. **162**:324 (June) 1944.

This article contains the description of a temporary change in the chin of newly born infants.

AUTHORS' ABSTRACT.

Acute Contagious Diseases

CONGENITAL CATARACTS FOLLOWING RUBELLA IN PREGNANCY. ARLINGTON C. KRAUSE, Ann. Surg. **112**:1049 (Dec.) 1945.

Nonmedical persons have regarded rubella as a mild disease which needs little or no treatment. The author in a review of the literature on the effects of rubella in pregnancy has shown that married women have reason for concern if they acquire rubella early in pregnancy. The ratio of infants with congenital defects to those with no defects born of mothers with rubella is too high to be disregarded.

Of the infants who had congenital abnormalities, the mothers generally dated their rubella before the fourth month of pregnancy. The infants frequently had more than one organ affected. The disease early in pregnancy, from the first three weeks to the end of the third month, tended to damage the eyes of the infant. Cataract was the common ocular disease.

It is questionable whether rubella can affect the fetus if the woman has the disease just before pregnancy.

Treatment should be considered for women with a questionable pregnancy or a pregnancy of the first three months with a history of rubella. The only possible but presumptive method of treatment seems to be the use of convalescence serum from patients with german measles.

A report on 5 cases of rubella seen at the University of Chicago in which congenital anomalies occurred in infants is presented by the author.

BANTIN, Omaha.

POLIOMYELITIS AND RECENT TONSILLECTOMY. JOHN A. ANDERSON, J. Pediat. **27**:68 (July) 1945.

By means of a questionnaire sent to 334 physicians in the state of Utah concerning the relationship of recent tonsillectomies to the occurrence of bulbar poliomyelitis, the following information was obtained:

The incidence of poliomyelitis after 4,199 tonsillectomies done during the epidemic period was found to be 0.404 per cent, or 2.62 times greater than the incidence of poliomyelitis in the child population of the same age. In 17 of 39 cases of bulbar or bulbospinal poliomyelitis the disease was preceded by a tonsillectomy done within thirty days of the onset of the disease.

This study indicated that a child on whom a tonsillectomy is performed during an epidemic of poliomyelitis has a sixteen times greater chance of contracting bulbar or bulbospinal poliomyelitis than a child of the general population.

AUTHOR'S SUMMARY.

PARALYSIS OF THE ESOPHAGUS FROM DIPHTHERIA. P. SEDALLIAN and P. MOUNIER-KUHN, Presse méd. **53**:185 (April 14) 1945.

In 50 of a series of 440 cases of diphtheria, the disease was complicated by paralysis. The esophagus was involved in 10 cases, the same number as of pharyngeal paralysis. There were 44 cases of paralysis of the soft palate, 23 cases of polyneuritis of the extremities, 18 cases of paralysis of accommodation, 4 cases of paralysis of the extrinsic muscles of the eye and 3 cases each of facial paralysis and laryngeal weakness. Esophageal paralysis was never an isolated finding, and in all but 1 case was seen in a triad with paralysis of the soft plate and pharyngeal paralysis. It seems to occur only in the cases of severe angina. No case was observed of the paralysis in childhood, although the authors recall the case of an infant who died shortly after admission with signs suggestive of esophageal paralysis.

Paralytic dysphagia appears during the third week following the sore throat. Liquids can be swallowed (sometimes with regugitation), but a bolus of solid food descends slowly. This can be demonstrated by fluoroscopy. Pharyngeal paralysis, hypesthesia of the subglottic, pharyngeal, laryngeal and esophageal areas and an accumulation of saliva in the pyriform sinuses can be shown by examination of the pharynx and the larynx.

In some cases the upper portion of the stomach may be involved. This is suspected in the absence of vomiting or when there is a constant feeling of fulness, and can be demonstrated by fluoroscopy.

Prognosis is good, the paralysis clearing within a few months. Slightly thickened feedings are given, and gavage sometimes is necessary. Bronchopneumonia

may ensue as a result of the pharyngeal-laryngeal hypesthesia. The mechanism is uncertain, but seems to be in the involvement of the sympathetic chain about the esophagus as well as of the vagus nucleus.

DAFFINEE, Melrose, Mass.

THE CENTRAL NERVOUS SYSTEM IN DIPHTHERIA. C. deLange, Ann. pædiat. **165**:225 (Nov.) 1945.

In 4 cases of diphtheria, in 3 of which there was a positive culture and in 1, though the disease closely resembled diphtheria, there was a negative one, the author made a microscopic investigation of the brain. The results were compared with those obtained in the examination of a patient with encephalitis following a subcutaneous injection of anatoxin.

In 1 of the cases in which there was a positive culture left-sided convulsions occurred during life; microscopicaliy only hyperemia and vasodilatation were found. In the other 3 there was an inflammatory process showing in cuffs of uninuclear cells (microglia) round the blood vessels, in neuroglia.

This process proved to be localized in the midbrain, in the pons varolii and in the tegmentum, in the bulb and in the pars superior of the cervical cord (more caudal parts of the cord not being available for an examination). The nerve cells generally proved to be intact, also the nerve roots and the efferent nerve fibers, as far as they were visible. The paralyses and the pareses observed during life therefore were not satisfactorily explained by the microscopic changes.

The histologic aspect of the brain in the encephalitis after subcutaneous injection of anatoxin closely resembled the foregoing findings, although there were minor differences.

Future observations and investigations must indicate whether anatoxin may exceptionally be able to produce an encephalitis or to activate another latent virus in the brain.

An extensive examination of the literature has shown the author how often and in how many different ways the brain and also the cord may be affected in diphtheria.

AUTHOR'S SUMMARY.

THE WATERHOUSE-FRIDERICHSEN SYNDROME. POUL KIRKETERP, Nord. med. (Hospitalstid.) **24**:2064 (Nov. 17) 1944.

Three children, aged 5 months, 2 years and 8 months and 3 years respectively, fell ill with fatal meningococcic sepsis. They displayed the clinical picture of the syndrome of Waterhouse and Friderichsen. Postmortem examination disclosed adrenal hemorrhage only in the first child. The author concludes that adrenal hemorrhage does not play any important role in the development of the symptoms.

WALLGREN, Stockholm, Sweden.

Acute Infectious Diseases

COMPLICATION OF TYPHOID BY PERFORATION OF HOLLOW VISCERA. RAMÓN POUS ROCA and LUIS TORREGROSA F., Bol. méd. d. hosp. inf., México **2**:275 (Nov.-Dec.) 1945.

The authors have taken the data for this paper from the files of the Hospital del Niño from July 1, 1943, to Aug. 15, 1945.

There have been 298 patients with typhoid, 3.2 per cent of the total number hospitalized. Out of those, there were 22 patients (7.4 per cent) with intestinal perforations or ruptures of the gallbladder. The authors explain the basis for the diagnosis, discuss the symptoms, the progress, etc., and the surgical treatment which is given as soon as the diagnosis is made, followed by appropriate medical treatment.

After reviewing the foreign literature on the subject and comparing it with the data of the Hospital del Niño, the authors find that this hospital has a higher percentage of these complications, a circumstance due in part perhaps to the malnourishment of the Mexican people as a whole and to the noxious habit of administering purgatives or enemas to patients with typhoid.

A capable physician who receives a patient early should be able to avoid these complications.

MADERO, México, D. F., Mexico.

A CASE OF TYPHOID AND TYPHOID MENINGITIS. PEDRO D. MARTÍNEZ and MAXIMILIANO SALAS, Bol. méd. d. hosp. inf., México **2**:301 (Nov.-Dec.) 1945.

J. R. R., an 8 year old girl, was admitted to the hospital complaining of malnourishment, dehydration, fever, tachycardia and somnolence. The first diagnostic impression was of typhoid, typhoid bronchopneumonia and congestive otitis on the right side. There were a positive Kernig sign, stiffness of the neck and a positive Brudzinski sign. In the hemoculture, Eberthella typhosa was identified. The spinal fluid was turbid and yellowish, with 142 mg. of proteins. The reaction to the Pandy test and the Nonne-Appelt reaction were positive. There were 3 mg. of sugar and 16 white cells, and the E. typhosa was cultured. The agglutination tests elicited positive reactions to both H and O antigens.

The patient died six days after admission. The pathologic studies confirmed the main diagnosis.

MADERO, México, D. F., Mexico.

Chronic Infectious Diseases

ANATOMOPATHOLOGIC CONFIRMATION OF ATELECTASIS IN INFANTILE EPITUBERCULOSIS. GUILLERMO LLODRA B. and ALBERTO GUZMAN, Rev. chilena de pediat. **16**:97 (Feb.) 1945.

Observations at autopsy are presented for 17 cases in which characteristic clinical and roentgenologic features, often described as "epituberculosis" or "perifocal pulmonary infiltration," were exhibited.

Areas involved were: upper lobe of the right lung, once; part of the upper lobe of the right lung, four times; median part of the lung, once; part of the median, four times; lower lobe of the right lung, once; part of the upper lobe of the left lung, once; lower lobe of the left lung, three times. True plugs of exudate were found in the bronchi in "half" of the cases; in 1, obstruction was due to rupture of a caseous node into the bronchus. In all, adhesions of nodes to adjacent bronchi were found in the zone of atelectasis.

Nine of the seventeen atelectatic areas contained a primary focus. Twice the primary focus was separate but in the same lobe; in 4 cases it was found in another lobe. Pathologic features suggested great variation in the duration of these lesions, but all lesions were caused by the narrowing of the bronchial lumen initiated by peribronchial adenopathy.

PLATOU, New Orleans.

STUDY OF 308 CASES OF CONGENITAL SYPHILIS OBSERVED IN THE YEARS 1935 TO 1939. PETER KRAG and ESTHER DALSGAARD-NIELSEN, Ugesk. f. læger **106**: 523, 1944.

The value of the Wassermann reaction in the testing of navel blood is slight. A negative result does not exclude syphilis. A thorough examination and observation of the infant with repeated tests of the blood is necessary. The Wassermann reaction is of no prognostic value at birth. In general, syphilis in infants is diagnosed in maternity hospitals, children's hospitals and dermatologic departments, while syphilis in children aged 1 to 14 years is diagnosed in dermatologic departments and by practitioners and that in subjects above 15 years by ophthalmologists. Half of the children in the present study displayed at least two characteristic signs, usually deformities of the teeth and bones, cutaneous diseases and diseases of the

mucous membranes. The triad of Hutchison is not frequent. More than one third of the infants died from syphilis or its complications during the first year of life. Most of the mothers were not treated during pregnancy. Ninety per cent of the children had positive Wassermann and Kahn reactions. An infant suffering from bullous syphilis had no Wassermann reaction, although spirochetes were demonstrated. Patients whose syphilis was detected at the ages of 5 to 10 years almost always had extremely strong seroreactions. The effect of prophylactic treatment during pregnancy was distinct; 81 per cent of the treated mothers but only 3.5 per cent of the untreated mothers had healthy babies.

WALLGREN, Stockholm, Sweden.

Diseases of Blood, Heart and Blood Vessels and Spleen

TWO CASES OF SO-CALLED MYXOFIBROMA OF THE HEART VALVES PRODUCING CLINICAL SYMPTOMS AND CONGENITAL VITIUM. ERIK JACOBSSON, Ann. pædiat. **161**:1 (July) 1943.

In addition to 2 cases of so-called myxofibroma of the heart valves of infants, who lived respectively twenty-six days and five and one half months and in whom there were clinical signs of congenital organic involvement of the heart, the author reports 2 cases of myxoma of newborn infants published earlier. A table of previously known cases of similar formations of the heart valves is given; 2 cases in which clinical signs were found are reported especially. The possibility of the lesions being the basis of a congenital organic disease of the heart is stressed.

AUTHOR'S ABSTRACT.

PHOSPHATASE CONDITIONS OF ERYTHROCYTES IN ANEMIA. URSULA RUST-BRUNNER, Ann. pædiat. **162**:30 (Jan.) 1944.

The erythrocyte phosphatase, measured as nearly as possible under natural conditions, gives values which, related to the same number of erythrocytes, show an age curve. In umbilical blood and in the blood of the newly born, the values are high; they sink quickly, however, to increase again in old age. In anemias with lively regeneration this increase is missing. An attempt is made to explain the differences found by the diversity of the sensitivity of the enzyme bound to the cell structure (in the sense of Willstätter).

It was incidentally discovered that O. Göbell's claim, concerning error in the determination of phosphate according to the recognized methods, is not valid.

AUTHOR'S ABSTRACT.

THREE NEW SYMPTOMS AS CLINICAL GUIDES IN DIAGNOSIS OF LUNG DISEASE IN CHILDREN. E. MAYERHOFER, Ann. pædiat. **162**:204 (April-May) 1944.

1. The simultaneous observation of the "mamillary symptom" (pigmentation, swelling), the "positive skin phenomenon" (thickening, callosity), and an eventual "unequal Pirquet reaction" (local hyperergy) provides a new triad of signs pointing at first sight to unilateral pulmonary processes (specific or nonspecific).

2. The mamillary and also the cutaneous symptom are distant reflexes, most probably originated by the vegetative nervous system.

3. The observation of these three signs is most important for the practitioner, the school physician and those for whom roentgenologic assistance is not always available.

4. In medical training the manner of clinical reflection described means a revival of exact clinical observation, whereby the "less interesting" cases awaken more interest to the profit of both patient and doctor.

AUTHOR'S ABSTRACT.

NIEMANN-PICK DISEASE: REPORT OF A CASE. NICOS FACATSELLI, Ann. pædiat. **162**:218 (April-May) 1944.

Clinical-biologic study was made of a 14 month old girl of healthy parents and non-Jewish extraction with Niemann-Pick disease. Puncture of the spleen, the bone marrow and the inguinal lymphatic glands showed typical foam cells. The chemical nature of the lipids could be determined microchemically from the puncture of the spleen of the living child. Phosphatides were present. There is a short discussion of the relations of Niemann-Pick disease to that of Gaucher and to the amaurotic family idiocy of Tay and Sachs.

AUTHOR'S ABSTRACT.

A NEW REACTION BETWEEN BLOOD SERUM AND HAYEM SOLUTION. MARTIN DU PAN, Ann. pædiat. **162**:229 (April-May) 1944.

1. The invention of a new nephelometric method for the quantitative determination of the reaction between definite quantities of Hayem's solution and serum is explained.

By marking the six different concentrations of the serum (7, 14, 21, 28, 35 and 42 per cent) on the abscissa and the values obtained from the galvanometer on the ordinate, a definite curve is obtained.

2. In normal persons the curve shows a maximum at 21 per cent or 28 per cent, while the galvanometer values vary between 22 and 44. In children under 2 years, the curve is lower than in adults; it is, on the contrary, normal in umbilical cord blood. The serum in pregnancy, ante partum, gives a lower and flatter curve.

3. The curve is higher in hepatitis, showing a maximum at 35 per cent. In nephrosis the curve is rather flat.

4. A chemical study of the reaction between Hayem's solution and serum has shown that only the globulin is precipitated with the Hayem solution, and that the change in the curve is probably due not to an increase or decrease of all or of a part of the globulins, but to an alteration in the nature of the globulins.

AUTHOR'S ABSTRACT.

SPLENOGENIC MALIGNANT LEUKOPENIA. PER SELANDER, Ann. pædiat. **162**:327 (June) 1944.

The author describes 2 cases of a fairly well defined symptom complex, the chief elements of which are chronic leukopenia, enlargement of the spleen, fever and anemia. In both cases healing took place promptly after extirpation of the spleen.

AUTHOR'S ABSTRACT.

THE POSSIBILITY OF INFECTION IN ACUTE HEMOLYTIC ANEMIA (LEDERER) PROVED BY TWO CASES IN SUCCESSION. ANNA SCHOO, Ann. pædiat. **163**:51 (July) 1944.

Schoo describes 2 cases of acute hemolytic anemia (Lederer) in 2 infants 5 months and 6 weeks old respectively. At the time of admission to the hospital of the first infant for acute hemolytic anemia (Lederer), the second child was being nursed for obstipation in the same room; she showed the first symptoms of the illness after twenty-five days. Infection was probable.

AUTHOR'S ABSTRACT.

CASE OF ATYPICAL ACUTE LEUKEMIA. S. T. HULTMAN, Nord. med. (Hygiea) **21**:15 (Jan. 2) 1944.

The author reports a case of acute leukemia in a boy of 9 years. During the first seven months of illness, the disease displayed symptoms and signs of severe anemia without any signs of leukemia. Repeated sternal punctures did not disclose

the true nature of the anemia until fourteen days before death, which occurred eight months after the first manifestation of the disease.

WALLGREN, Stockholm, Sweden.

IRON TREATMENT OF ANEMIC AND OF NONANEMIC INFANTS AND ITS INFLUENCE ON THE MICROCYTOSIS. H. KREUTZFELDT, Nord. med. (Hospitalstid.) **21**:378 (Feb. 25) 1944.

Medication with iron preparations during one to three months for children with hypochromic, microcytotic anemia influences in a certain degree but does not normalize the hypochromic and microcytotic state. This medication for healthy children of the same age (3 months to 1 to 2 years) is followed by a slight rise of the hemoglobin content, provided the content before treatment was below 90 per cent (12.5 Gm.), but does not influence the size or hemoglobin content of the single blood corpuscle. The Price-Jones curves of healthy children are not altered significantly after medication with iron.

WALLGREN, Stockholm, Sweden.

PAROXYSMAL TACHYCARDIA IN INFANTS. JÖRGEN FLAMAND CHRISTENSEN, Nord. med. (Hospitalstid.) **22**:797 (April 28) 1944.

Paroxysmal tachycardia is not infrequently overlooked in infants because the onset of the attacks usually is not characteristic. The symptoms are loss of appetite, restlessness, perhaps vomiting and diarrhea. Many attacks cease spontaneously. During the attacks, the cardiac rate is from 250 to 300, and there may be alarming symptoms of heart failure and possibly collapse, convulsions and loss of consciousness. The attacks may occur in patients with congenital heart disease, but in infancy it is frequently impossible to find any underlying pathologic condition. The prognosis after a single attack is favorable. Usually the attacks occur for short periods only, but even if they recur constantly the children will develop well if their state of health is not impaired by congenital heart disease or a like condition. Digitalis, strophanthin and mecholyl have been found the most effective drugs for treating the disease. The author illustrates his article with reports of 2 cases: 1. The first was that of a boy who had his first attack of paroxysmal tachycardia at 3 weeks of age (heart rate 300). No signs of cardiac involvement were revealed. In all he had only two or three attacks and his later development was normal. 2. The second was a boy who had his first attack of tachycardia at 6 months (heart rate 320). During the following six months he suffered from six attacks in all of paroxysmal tachycardia; then he was free from symptoms and displayed normal development. His heart was normal clinically and the electrocardiogram and roentgenologic examination showed normal conditions.

WALLGREN, Stockholm, Sweden.

A CASE OF STENOSIS OF THE SPLENIC VEIN. G. KLACKENBERG, Svenska läk.-tidning. **41**:249 (Jan. 28) 1944.

A girl of 5½ years with splenomegaly and uncharacteristic abdominal symptoms displayed leukopenia, slight oligochromemia and prominent dilatation of the esophageal veins. She had not suffered from bloody vomiting. A splenectomy was performed, and the girl was discharged in good condition. The spleen showed cirrhotic changes due to chronic stasis. Its weight was 265 Gm.

WALLGREN, Stockholm, Sweden.

FOOD RESTRICTIONS AND THE RED BLOOD CORPUSCLES. BO VAHLQUIST and GÖSTA NEANDER, Svenska läk.-tidning. **41**:1327 (May 12) 1944.

In the year 1943 the mean value of hemoglobin (11.52 Gm.) of infants 6 to 12 months old showed a statistically significant decrease as compared with the year

1939 (12.33 Gm.). This depression of the hemoglobin values is probably due to deficiency of iron, as it was compensated by medication with preparations of iron.

WALLGREN, Stockholm, Sweden.

THE HEMOGLOBIN CONTENT OF THE BLOOD IN SMALL CHILDREN. SVEN AGNER, Ugesk. f. læger **106**:380, 1944.

Four hundred and thirty children belonging to day nurseries and play schools were examined during the spring and 382 children during the autumn. The hemoglobin per cent during the spring was 84.7 plus or minus 4.2 and during the autumn was 87.3 plus or minus 4.8 per cent. There were no distinct differences in differnt ages and different sexes. Two hundred and seventy-six children who were examined both in the spring and in the autumn showed an increase of the hemoglobin content in the autumn.

WALLGREN, Stockholm, Sweden.

MALIGNANT TYPE OF GAUCHER'S DISEASE. TAGE ESPERSEN, Ugesk. f. læger **106**: 1143, 1944.

A boy, 1 month old, displayed symptoms and signs of Gaucher's disease and died two months later. Thrombopenia, hemorrhagic diathesis and enlargement of the liver and spleen were observed.

WALLGREN, Stockholm, Sweden.

Diseases of Nose, Throat and Ear

A CROSS-CULTURAL APPROACH TO THE PROBLEM OF STUTTERING. ADELAIDE KENDALL BULLEN, Child Development **16**:1 (March-June) 1945.

In attempting to explore the problem of possible causes of stuttering, material from this culture has been examined in the light of data from three nonliterate societies: the Navaho Indians in the United States, the nonliterate societies in New Guinea and Australia and the Eskimoes in Greenland.

Data presented included medical, psychologic, sociologic and anthropologic findings.

[CHILD DEVELOPMENT ABSTRACTS]

RELIABILITY OF INFANT SPEECH SOUND DATA. ORVIS C. IRWIN, J. Speech Disorders **10**:227, 1945.

The author suggests that studies of data on infant speech sounds may be improved by statistical investigation. First, ranking order correlations were obtained from a sample of 1,047 records of speech sounds of infants from 1 to 30 months of age. Two records were selected per month, 60 in all. Each record includes the sounds recorded during thirty expirations by a given infant. The results show the consistency of the sample randomly drawn. Second, the method of percentage of agreement offered a more detailed analysis of the reliability of the data. Third, adequacy of the size of the sample by range of value and number and by percentage of value is greater than .70. Another sample was made with 64 records, ranging from the third to the thirtieth month. Satisfactory reliabilities were obtained by these various methods.

PALMER, Wichita, Kan.

MEDICAL FOLLOW-UP OF HEARING TESTS. COURTNEY D. OSBORN, J. Speech Disorders **10**:261, 1945.

Two audiograms were taken a year apart for 248 children with 327 ears the hearing of which was defective. These children had received no medical attention previous to a hearing conservation program. The group was divided into two parts, those who received medical attention afterward and those who did not. The first and second audiograms were analyzed to compare gains and losses. Of

the group of ears receiving medical treatment after the case-finding program, 85 per cent showed improvement in hearing, 65 per cent of these to the range of "normal" hearing. Of the group of ears receiving no medical treatment, 23 per cent showed some improvement in hearing, 11 per cent of them to the range of "normal" hearing. Only 14 per cent of the group receiving medical treatment showed no change in hearing loss, and none of them had a greater loss at the second testing. This indicates that the hearing of school children can be conserved through careful testing programs with emphasis on a medical follow-up. The author believes that public education in hearing conservation is badly needed and should be the primary objective in a hearing conservation program.

PALMER, Wichita, Kan.

TREATMENT OF A CHILD WITH DELAYED SPEECH. LORNA SHOGREN WERNER, J. Speech Disorders **10**:329, 1945.

The history and method of treatment of a 5 year old girl who had never uttered a sound are reported. She was intelligent and interested in her environment but gave the impression of being an abnormal child in appearance, behavior and lack of speech. Her first word was "boom" in imitation of noises. It was not possible to do any direct stimulus of speech. She apparently was badly inhibited.

PALMER, Wichita, Kan.

METHODS FOR TEACHING (R) TO THE GERMAN ÉMIGRÉ. MORRIS COHEN, Quart. J. Speech **31**:214, 1945.

The student is instructed to place the tongue in position for *r* and attempt to pronounce it with great vigor, meticulously imitating the instructor. He should be made to hold this *r* four to five times longer than usual because it is helpful for his own ear to hear this. Students should not be allowed to think a great deal about the process, but should be given practical instruction. Words in which the *r* is in the second syllable with an accent are easier to say than those with *r* in the first syllable. Some students find it easier to acquire the pronunciation of *r* if it is preceded by a voiceless consonant. Guttural sounds such as *k* and *g* interfere with acquiring *r* and should be avoided until its pronunciation is definitely established.

PALMER, Wichita, Kan.

THE SEMANTIC ASPECTS OF STUTTERING IN NON-STUTTERERS: ADDITIONAL DATA. JESSE J. VILLARREAL, Quart. J. Speech **31**:477, 1945.

One hundred and fifty-four males and 117 females—all normal speakers—were given the following questionnaire: 1. Did you ever have a stuttering defect in speech? 2. Did any one ever call you a stutterer? 3. Did any one ever say you were stuttering? 4. Do you think you ever said anything stutteringly? 5. Do you think you have a habit of stuttering? 6. Did you ever call yourself a stutterer? The data in general reproduced those originally reported by Voelker: fourteen per cent of the subjects had had a stuttering defect of speech, and 6.7 per cent had been called stutterers; 29.1 per cent had been said to have been stuttering; 76 per cent thought they had spoken stutteringly; 1 per cent thought they still had the habit; 9.9 per cent had called themselves stutterers. The data for the most part are sex-differentiated. Almost twice as many males, for example, have been said to have been stuttering as females.

PALMER, Wichita, Kan.

EMERGENCY TRACHEOTOMY. EDUARDO ECHEVERRÍA and CARMEN LABRA, Bol. méd. d. Hosp. inf., México **2**:261 (Nov.-Dec.) 1945.

The authors discuss the tracheotomies performed at the hospital, where the mortality had been 11 per cent. With a new technic introduced by them, in the last nine months, in 40 cases the fatality rate has been brought down to zero.

They first make a careful diagnosis, taking into account all the symptoms. The second step is the operative technic; the authors first do a direct laryngoscopy, which aids in the correct diagnosis, and then introduce a bronchoscope which is kept in place throughout the operation. The advantage of this procedure is evident from the moment the bronchoscope is placed: the dyspnea stops instantly, and the child ceases to be restless and often falls into a placid sleep. Then, with the respiration assured, an unhurried low tracheotomy is done, in which all the small details can be comfortably attended to. The anesthetic used is a 0.5 to 1 per cent solution of procaine hydrochloride, and in a small amount (not over 4 to 5 cc.). The next step has to do with the postoperative care. The nurse in charge must be well acquainted with all the details of a humid atmosphere, clean cannula, aspiration, etc. The patient must receive antidiphtheric serum, sulfonamide drugs, penicillin, etc., depending on the case. The cannula is removed carefully, but as early as possible.

MADERO, México, D. F., Mexico.

ASEPTIC MENINGITIS BY MASTOIDITIS: PRESENTATION OF A CASE. FERNANDO LÓPEZ CLARES and FERNANDO ESPINOSA OGARRIO, Bol. méd. d. hosp. inf., México **2**:325 (Nov.-Dec.) 1945.

R. M. J., a 12 year old boy, became ill eight days before his hospitalization, complaining of suppurative otitis of the left ear. On admission there were clinical signs of meningitis, which were later confirmed by the laboratory. There was a purulent discharge from the left ear, and the mastoid region of the same side was acutely inflamed.

The treatment was initiated with administration of sulfadiazine, 0.50 Gm. every four hours. Treatment with penicillin was instituted the next day. On that same day mastoidectomy was done on the left side. The progress was slow but uneventful, and the patient was discharged fifty-four days later.

The total dosage administered was 1,940,000 units of penicillin and 105 Gm. of sulfadiazine.

MADERO, México, D. F., Mexico.

SULFANILAMIDE TREATMENT OF ACUTE PURULENT OTITIS IN CHILDREN. FALBE-HANSEN and BECKER-CHRISTENSEN, Ugesk. f. læger **106**:163, 1944.

A sulfanilamide-treated group of patients with otitis media numbered 335 and a control group 323. The otitis was due to pneumococci, hemolytic streptococci and Pfeiffers bacillus. The secretion time was decreased 28 to 40 per cent by the treatment with sulfanilamide. Of the control group, 9.3 per cent were operated on; of the sulfanilamide-treated group only 1.5 per cent. Only cases which were of less than five days' duration were considered. The best result was noted within the first two days of the otitis.

WALLGREN, Stockholm, Sweden.

Diseases of Lungs, Pleura and Mediastinum

ACID-FAST BACILLI IN NONTUBERCULOUS PULMONARY DISEASE. RICHARD A. S. CORY, Am. Rev. Tuberc. **52**:36 (July) 1945.

Since Koch's discovery of the tubercle bacillus it has been generally considered that the presence of acid-fast organisms in the sputum from a case of pulmonary disease indicates tuberculosis. The authors warns, however, against regarding an isolated positive result in a picture otherwise atypical clinically as final proof of the presence of tuberculosis.

Acid-fast saprophytes have been found in water, butter, grass, smegma, feces and milk. They are extremely common and widespread in nature and can appear in lesions in man even though they have probably played no real part in the causation of such lesions. These organisms occurring in cases of nontuberculous pulmonary disease so distort the picture as to make the diagnosis difficult until their true nature has been determined by animal inoculation.

Two cases are reported, 1 of a fetid abscess of the lung and 1 of an atypical pneumonitis. In both these cases the sputum was returned with a positive result on culture for tubercle bacilli. In the former the acid-fast organisms were proved by animal inoculation to be nonpathogenic, and in the latter the condition resolved so rapidly as to render the diagnosis of tuberculosis untenable.

The author urges a more critical attitude toward positive results of cultures in otherwise atypical cases, unless these results are backed up by definitely positive findings as a result of animal inoculation.

SMITH, Ogden, Utah.

LYMPHOSARCOMA OF THE MEDIASTINUM IN A CHILD: RESULTS WITH RADIATION THERAPY; NINE YEAR FOLLOW-UP STUDY. B. KAUFMAN, Arch. Pediat. **62**:340 (Aug.) 1945.

A case of mediastinal lymphosarcoma with multiple metastases is reported. The original tumor present at birth and subsequent secondary tumor masses were treated by high voltage roentgen therapy. The author observed a greater resistance of the metastatic lesions to treatment with roentgen rays than had been encountered in the primary tumor, and he suggests that even more intensive high voltage roentgen therapy probably was indicated.

GRULEE, JR., Minneapolis.

BROWN INDURATION OF THE LUNG AND CHILDHOOD'S SECONDARY ANEMIA. S. SCHEIDEGGER and A. DREYFUS, Ann. pædiat. **165**:2 (July) 1945.

The observation of a brown induration of the lung in the case of a 1 year old girl is discussed. The manifestation appeared clinically in the fourth month, with periods of fever, atrophy, severe anemia and signs of focal nephritis. The skin was strikingly brown.

The morbid anatomic changes were brown induration of the lung due to congestion, and slight hemosiderin storage in the lymph glands. The heart chamber on the right side showed hypertrophy and at the same time slight myocarditis, with scars and fatty degeneration. In the kidney too a process of inflammation was present. For the source of the pulmonary bleeding, one must consider a process of inflammation, and the concept of primary congenitally predisposed weakness must be indicated as unproved.

AUTHORS' ABSTRACT.

DECREASE OF PHOSPHORUS IN PNEUMONIA, IN RELATION TO THE ADMINISTRATION OF ONE LARGE DOSE OF VITAMIN D. A. J. J. RODENBURG, Maandschr. v. kindergeneesk. **10**:142 (Jan.) 1941.

In 27 of 53 children suffering from varying forms of pneumonia a decrease of the inorganic phosphorus content of the blood serum was found. The possibility of a rachitic or nonrachitic causation is discussed. Therapy by administration of one massive dose of vitamin D_2 (calciferol) and vitamin D_3 (activated 7-dehydrocholesterol) was applied as well in pneumonia as in rickets, and the results were compared.

S. VAN CREVELD, Amsterdam, The Netherlands.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

A QUANTITATIVE STUDY OF SALIVA GLUCOSE. MAURICE L. BLATT, MAXIMILIAN KERN and CECELIA M. KORTUEM, J. Pediat. **27**:71 (July) 1945.

The children observed in this study were under 42 months of age, had deciduous teeth, all free of caries, and they lived in an institution under identical environmental conditions. This group was ideal for this basic study, since saliva sugar values were obtained for children with good oral hygiene and free of caries, and the assay was not influenced by the forming of lactic acid or by other sugar-reducing micro-organisms lodged in carious pockets. It seemed reasonable to

assume, therefore, that the assay of saliva sugar in this group was a fair sample of primary and basic values.

A wide irregular variability occurred in the percentage of saliva sugar when assays of subjects were compared under the same test conditions. In a few instances, irregularity was found in the same child in the four tests, but in general the trend of saliva sugar was upward following the ingestion of dextrose and downward fifteen minutes later. This trend was confirmed by the arithmetic means in table 1 and the graph line in figure 1. An equally interesting observation made from the table was the frequent and certainly unexpected divergence in concomitant blood–saliva sugar assays. The individuality of results does not allow a ratio formula, although the mean curves of the two assays are similar. The contemplated continuation of the study with more cases may solve this difficulty.

These irregular findings seem to us to be of more than academic interest in their possible relationship to the cause and production of dental caries, since dental caries is reported by many authors to occur equally irregularly among the members of families and of racial groups. Blayney suggests as one of the extrinsic factors in the production of caries the "fermentable substance in saliva and tissue fluids." Glucose falls in this category, and it is possible that individual variations in the saliva content of this substance may be related to the individual variants in the incidence of caries. However, numerous investigators express the same opinion that Boyd does in his conclusion that "sugar or starch has not been observed to favor caries, unless use of either materially diminished the amounts of ingested protective foods." The group studied at St. Vincent's Infant and Maternity Hospital was on what is usually considered an adequate diet, and in spite of the comparatively large amount of sugar in the saliva of some of these infants, none had caries. This seems to substantiate Boyd's observations.

AUTHORS' SUMMARY.

GLYCOGEN STORAGE DISEASE. EDWARD M. BRIDGE and L. EMMETT HOLT JR., J. Pediat. **27**:299 (Oct.) 1945.

Two patients with glycogen disease have been studied. Both children, aged 16 months and 5½ years respectively, presented the usual picture of enlarged liver, fasting hypoglycemia and ketosis and slight hyperglycemia after the injection of epinephrine. The older child was also dwarfed. Material obtained by biopsy, the blood and the urine were studied, and observations on general metabolism were made in a metabolism chamber.

Biopsy showed the liver to be loaded with glycogen (15.4 per cent and 13.9 per cent) which was stable when allowed to stand at room temperature, but was broken down when mashed with normal liver or incubated with a buffered solution of pancreatic amylase. Muscle glycogen was extremely high (4.7 per cent) in the older child but normal in the younger one. Sections showed the hepatic cells to be greatly distended with glycogen and to contain only small amounts of cytoplasm.

Blood glycogen was increased and was present almost entirely in the blood cells. Reprecipitation of this "glycogen" gave a substance that reacted in every way like normal hepatic glycogen.

Metabolic studies on the younger patient showed a normal level of respiratory quotient between feedings. However, if the interval between feedings was more than four hours, the respiratory quotient decreased rapidly and within two hours was below 0.80. Corresponding to this rapid fall, the blood sugar also decreased to hypoglycemic levels. Thus, in spite of a liver known to contain excessive quantities of glycogen, the child reacted to starvation in a way suggestive of almost complete absence of carbohydrate reserves. In the older child, evidence was obtained which suggested that food carbohydrate was rapidly converted into fat to compensate for the absence of storage space in tissues which were already filled with glycogen.

The nitrogen balance of the older child was found to be negative. It is suggested that this loss of nitrogen results from the increased glyconeogenesis which develops to compensate for the hypoglycemia and useless glycogen stores. Such a negative nitrogen balance offers a possible explanation for the retarded skeletal development.

Clinical improvement followed the use of a diet which was high in protein and given in four meals, one of which was offered at midnight.

In conclusion, it is felt that the various manifestations of glycogen disease can be understood as secondary or tertiary reactions to the central inability of the organism to mobilize its glycogen stores.

AUTHORS' SUMMARY.

INTESTINAL RESECTION (125 CM. OF ILEUM AND 25 CM. OF SECUM AND ASCENDING COLON): STERCORAL FISTULAS AND EVENTRATION COMPLICATED BY MALARIA VERIFIED ONLY IN THE MARROW. J. LOZOYA, F. CISNEROS and G. ZÁRATE, Bol. méd. d. hosp. inf., México **2**:313 (Nov.-Dec.) 1945.

R. M. A., a 9 year old boy, was operated on for appendicitis three weeks previous to his admission. At the admitting office he was found to have an eventration of the cecum and of part of the ileum.

Seven days after hospitalization, stercoral fistulas developed, in spite of the care taken to avoid them. After the routine examinations and preoperative care, the child was operated on. The authors found a great number of thick adhesions which glued into one large mass most of the abdominal organs. It was this circumstance that forced the authors to resect a large portion of the intestine. The patient responded favorably to the routine postoperative therapeutic treatment.

The progress was uneventful, except that the patient was losing weight and that the anemia was more pronounced. A bone marrow count done one month after the operation revealed 570 Plasmodium vivax organisms per cubic centimeter. These disappeared with a correct and intensive malarial treatment.

The patient was discharged completely cured.

MADERO, Mexico, D. F., Mexico.

CONGENITAL STENOSIS AND DILATATION OF THE ESOPHAGUS: DIFFUSE SUPPURATIVE APPENDICITIS. JESÚS ALVAREZ DE LOS COBOS and MAXIMILIANO SALAS, Bol. méd. d. hosp. inf., México **2**:319 (Nov.-Dec.) 1945.

F. J. F. Z., an 8 month old boy, was admitted complaining of projectile vomiting from the age of 1 month.

Physical examination indicated severe malnourishment and slight dehydration. No pyloric tumor was found. Vomiting was observed, but was not projectile; it was rather an overflow. This, together with the roentgenologic studies, make the first part of the diagnosis.

The night of his hospitalization, the child began to have a series of bloody vomits after one of which, next morning, he suddenly died.

The necropsy revealed the presence of a congenital hernia of the stomach through the esophageal hiatus which caused the stenosis of the esophagus with secondary dilatation of that organ. Also, a diffuse suppurative appendix was found, which may have been the immediate cause of death.

MADERO, Mexico, D. F., Mexico.

Nervous Diseases

CHRONIC LEPTOMENINGEAL THICKENING FOLLOWING TREATMENT OF MENINGITIS WITH SULFA-DRUGS. PERCIVAL BAILEY, Ann. Surg. **122**:917 (Dec.) 1945.

Since the initiation of serum therapy of meningococcic meningitis various neurologic defects have been recorded as sequels to otherwise successful treatment

of the infection. As the infection is overcome the purulent exudate is organized by proliferation of fibroblasts which occlude the narrow pathways in the leptomeninx and obstruct the circulation of the cerebrospinal fluid.

The author reports 4 cases in which the acute infection was controlled or cured by the administration of sulfonamide drugs or penicillin, but the condition went on to death or some serious sequel.

BANTIN, Omaha.

DISCUSSION OF SUBDURAL HAEMATOMA IN INFANCY. Proc. Roy. Soc. Med. **38**:370 (May) 1945.

Commander R. Cannon Eley, U.S.N.R., stated that by subdural hematoma is meant simply a pocket of blood between the dura and the arachnoid membranes, the usual anatomic site being the frontoparietal area. He then took up in detail the symptoms; the establishment of a diagnosis of subdural hematoma by subdural tap, by lumbar puncture or by roentgenologic evidence as demonstrated by encephalography or ventriculography; differential diagnoses; the causation (trauma holds the first position in several theories that have been advanced; other factors which may be of importance are age, sex—60 per cent of patients have been males—infection, scurvy and malnutrition), and the pathology of the disease.

Dr. Janet Gimson then reported on 3 cases of subdural hematoma showing to some extent the diversity of symptoms which may occur in such cases.

WILLIAMSON, New Orleans.

Psychology and Psychiatry

AUTISTIC THINKING AS A "TRANSITORY PHENOMENON OF CHILDHOOD." GELOLO MCHUGH, Child Development **15**:89 (June-Sept.) 1944.

In the present study Moore's test was given to a group of 70 subjects, 10 at each age level, and it was found that, with what appears to be a definitely superior group of subjects, the ability to detect autistic fallacies increases gradually from the ages of 6 to 12 concomitantly with the development of ability to reason logically and to detect logical fallacies as determined by other tests of reasoning ability. No evidence was found to support Moore's contention that "Autistic reasoning is a transitory phenomenon of childhood," and it is contended that the acceptance and support of the two fallacies which furnished Moore's evidence is due to the fact that children come to accept the false premises as a result of experience and training rather than of development of reasoning ability.

[CHILD DEVELOPMENT ABSTRACTS]

MUSCULAR ACTIVITY AN AID IN CONCEPT FORMATION. SINA M. MOTT, Child Development **16**:97 (March-June) 1945.

A positive and direct influence of muscular activity on the formation of concepts is found on studying the growth of a concept as shown by the drawings of a man made over a period of three weeks by 24 American children ranging in age from 51 to 72 months. Each child, for ten successive school days, drew a picture of a man. After his attention was called to the head, the stomach, the arms, the legs, the fingers, the toes, the hair, the eyes, the nose and the mouth in the style of "This is the House that Jack Built," he drew a second series of ten pictures. After an intermission of six weeks in which the subject was completely dropped, the study was completed with the addition of the ears, the eyebrows, the neck, the shoulders and the tongue. The total of thirty drawings per child were then scored, and the results were tabulated. From these it is found that: (1) Each child made a positive increase of 1 to 10 points; (2) while the median of the scores on the twenty-first was lower than that on the twentieth it was higher than that on the first, and the loss was soon regained and progress continued, and (3) there was a positive and direct influence of the activity on the drawings which followed

it; for instance, 2 per cent of the drawings portrayed the neck before attention was called to it, while 52 per cent of the following drawings contained it.

[CHILD DEVELOPMENT ABSTRACTS]

THE SOCIAL INTERESTS OF YOUNG ADOLESCENTS. GERTRUDE HILDRETH, Child Development **16**:119 (March-June) 1945.

Activity preferences were indicated by 192 junior high school boys and girls on a 45 item interest inventory. The results were analyzed to discover the relation between age and preference for social interests of a heterosexual nature, e. g., dancing, having "dates," going to mixed parties. The activity preferences were classified into two groups: social activities on the one hand and all other preferences on the other. At the age of 10 years no differences between boys and girls were found, but in age levels 11 to 14 girls showed greater preference than boys for social activities participated in by both boys and girls. This difference became more noticeable with increase in age up to 14 years. These results tally with the established facts indicating the more rapid physiologic sex maturation of girls in contrast to boys.

AUTHOR'S SUMMARY.

SOME PSYCHOLOGIC HAZARDS IN THE ADOPTION OF A CHILD. MILTON E. KIRKPATRICK, New Orleans M. & S. J. **98**:285 (Dec.) 1945.

It has long been the opinion of the reviewer that too few physicians are aware of the responsibility they assume in becoming active participants in adoptions. The author points out these dangers clearly and concisely. The hazards of adoption should be borne by properly constituted sociolegal agencies. Regardless of how much information a physician may have concerning a child or the adoptive parents, he should never specifically recommend adoption. Always including a trial period of placement, he should merely point out the assets and liabilities involved. Having knowledge of a child apparently suitable for adoption, he should refer the parties concerned to the proper social agency. It is pointed out that the control of illicit traffic in babies requires that all adoptions should be a matter of public concern. The principles which should govern adoptions are set forth by the United States Children's Bureau. These are:

1. Adoption proceedings should be held before a local court accustomed to handling children's cases; petitioners for adoption should reside and be known locally.

2. The court should have the assistance of the state welfare department, which should be made a party to every adoption proceeding.

3. Consent to adoption should be obtained from natural parents or other persons or agency having legal responsibility.

4. Court hearings should be closed and records confidential.

5. A trial period of residence, preferably for one year in the adopted home, should be required prior to issuance of the final adoption decree.

6. Provision for removal of children from unsuitable homes should be made, as well as provision for their care and guardianship after such removal.

7. All applicable statutes should assure the welfare of the child and the rights and obligations of the parents.

BERKLEY, Beverly Hills, Calif.

Diseases of the Muscles, Bones, Joints and Lymph Glands

THE USE OF PENICILLIN IN THE TREATMENT OF ACUTE HEMATOGENOUS OSTEOMYELITIS IN CHILDREN. EDWARD L. COMPERE, WILLIAM J. SCHNUTE and LEE M. CATTELL, Ann. Surg. **122**:954 (Dec.) 1945.

In young children the infecting organism is more often the streptococcus. The initial infection may be in the nose, the throat, the middle ear, a vaccination wound

or the umbilicus of a newborn infant. In children from the age of 3 to puberty the hematogenous osteomyelitis is secondary in most cases to some small area of infection in the skin.

While the various sulfonamide compounds have been proved of value in the treatment, the authors feel that penicillin is a more effective agent. They advise for children 3 to 12 years old an intramuscular dosage of 15,000 to 20,000 units every three hours, day and night. After the temperature subsides the dose may be reduced to 10,000 units. After five days of normal temperature, the penicillin may be discontinued.

Twelve cases seen at the Children's Memorial Hospital in Chicago between July 1943 and March 1, 1945 are reported.

BANTIN, OMAHA.

Skin Diseases; Allergy

FIRST OBSERVATIONS ON THE TREATMENT OF KERION WITH ETHYL CHLORIDE. ANTONIO DUBÓN and HERMINIA HERNÁNDEZ, Bol. méd. d. hosp. inf. **2**:271 (Nov.-Dec.) 1945.

The authors begin this article with a description of the disease known as kerion and differentiate it from other tineas both from the pathologic and from the clinical point of view.

At the hospital there have been 13 patients with kerion treated by the authors. Out of these, 9 were treated with several medicaments, but 4 had relapses. The other 4 patients were treated exclusively with ethyl chloride in topical applications twice a day, with flattering results. There have been no relapses after two months of observation.

The authors do not recommend the use of ethyl chloride for the treatment of other varieties of tinea.

MADERO, Mexico, D. F., Mexico.

NICOTINIC THERAPY IN ALLERGIC DISTURBANCES. JULIUS SURÁNYI and STEFAN ZIMÁNYI, Ann. pædiat. **160**:69 (Jan.-Feb.) 1943.

Intracutaneous injection of nicotinic acid produces a wheal and flare, the duration of which is equal to that of the reaction to histamine, though the wheal and flare are smaller. A circular, broad, inflamed area is formed around the wheal and flare.

Given in doses of 0.05 to 0.15 Gm. once or twice daily as a three week treatment, the nicotinic acid has in most cases a beneficial effect on allergic diseases (asthma, spastic bronchitis, enteral allergy, urticaria, exudative eczema and hay fever).

The reactive reddening of the skin gradually recedes during the cure; after a shorter or a longer time, it reappears usually only during the first five to six days, occasionally appearing again several days later.

In some cases the reaction is accompanied with restlessness and severe itching and rarely with vomiting and a definite feeling of weakness.

During the treatment, there is in a larger number of cases loss of weight, which gradually disappears afterward.

The cutaneous effect is many times greater for a dose given on an empty stomach than for the same one after a meal.

After administration of nicotinic acid, the sudden reappearance of already extinguished allergic cutaneous reactions can occasionally be observed.

Therapeutic success lasts in some cases many months after treatment has ceased.

Owing to the relatively short time of observation, it is not possible to state the duration of the favorable effect at present.

AUTHORS' ABSTRACT.

Book Reviews

Kompêndium der topischen Gehirn und Rueckenmarksdiagnostik. By Robert Bing, Clinical Professor of Neurology, University of Basel. Twelfth edition. Price, 22 francs. Pp. 275. Basel, Switzerland: Benno Schwabe, 1945.

Ever since its first appearance in 1909 this book has had great popularity on the European continent and among German-reading physicians elsewhere. In the opinion of the reviewer this popularity is well deserved. For one thing, the subject matter is well organized, and the descriptions tend to correlate structure with function—a welcome departure from the dry accounts of nerve pathways usually found in the standard text books or in the more involved treatises on neurology. Another commendable feature of this volume is the omission of dilatory and extraneous discussions. The author, to put it in the vernacular, sticks to the point—a blessing to the "lay" (non-neurologist) reader.

This (twelfth) edition is considerably enlarged, and two new chapters are included: a comprehensive description of occlusion of cerebral vessels, and a detailed discussion of the localization of brain tumors of various histologic characteristics.

The pediatrician with a knowledge of German will find this book an excellent outline of clinical neurology and an invaluable help in interpreting lesions of the brain and spinal cord.

Hypno-Analysis. By Lewis R. Wolberg, M.D., with a Foreword by A. Kardiner, M.D. Price, $4.00. Pp. 342. New York: Grune & Stratton, Inc., 1945.

This is an excellent exposition and interpreted description of the processes of hypnosis and mental analysis. The first 135 pages are devoted to a description of the analysis of an extremely complex individual, who had had a rather unusual artistic training which gave him the symbolic attitude of the artist and perhaps, one might add, of the insane. Hypnotism was used to bring out symbolic values and to give some suggestion as to their importance and interpretation. Analysis of a psychoanalytic type is fully used and described. This case report is followed by a 20 page "Dynamic Interpretation" by Dr. A. Kardiner, whose thorough knowledge and considerable experience in the analytic field gives his interpretation its value. There are then another 180 pages about the theory and practice of hypnoanalysis. The chapters of greatest interest perhaps are those that deal with the relationship between the patient and the doctor. Their names are suggestive of the contents: "Hypnosis and the Transference," "Hypnosis and Resistance" and "Hypnosis and Interpretation." Of course this is Dr. Wolberg's chosen field, and his technic and the results would seem to indicate that in the hands of Dr. Wolberg this technic is extremely valuable. How successful other men using this technic would be is another matter. However, the book is a "must" for any psychotherapeutist.

The Physiology of the Newborn Infant. By Clement A. Smith, M.D. Price $5.00. Pp. 312, with 36 illustrations and 38 tables. Springfield, Ill.: Charles C Thomas, Publisher, 1945.

Dr. Clement Smith was Professor of Pediatrics at Wayne University College of Medicine and Medical Director of the Children's Hospital of Michigan. His book reflects his wide reading, deep study and excellent clinical experience. As is essential in a study of the newborn, the physiology of the fetus is also thoroughly covered.

In addition to the usual chapters on respiration, circulation, the digestive system and the blood, which are fully covered and well presented, the author has

delved deep into all aspects of metabolism, including heat regulation, assimilation and metabolism as related to specific food substances, vitamins and minerals, the regulation of electrolytes and water and the function of the endocrine glands as they affect nutrition and growth. Renal physiology is unusually well discussed, and an interesting chapter on neonatal immunity completes the book.

A wide range of investigative material has been brought together, and the extensive bibliographies at the end of each chapter give not only the author and reference but the exact title of the article. The index is also extremely complete. The book is well written throughout and should prove of great value to both clinician and research worker.

Nutrition and Chemical Growth in Childhood: Vol. II, Original Data. By Icie G. Macy, Ph.D., Sc.D., Director of the Research Laboratory, Children's Fund of Michigan. With a Foreword by Laurence Reynolds, M.D., and a Supplement by Julia Outhouse Holmes, Ph.D. Presenting Data Collected in the Department of Home Economics, Agricultural Experiment Station, College of Agriculture, University of Illinois. Cumulative Index. Price, $10. Pp. 433-1460, with 707 illustrations. Springfield, Ill.: Charles C Thomas, Publisher, 1946.

Volume 1 of this series has been reviewed previously in this journal (**65**:518 [March] 1943). It tells of the long term metabolic studies the author and her colleagues have conducted relating to normal children. As originally planned, volume II was to deal with the interpretation of the metabolic data. Instead, the current volume is limited in scope to the presentation of the records of 33 children who have served as subjects for the studies. A third volume, not yet published, will deal with the analysis and interpretation of the data.

More than half of the children were studied recurrently for periods of many months. Their records portray the progress of such children, each as a psychobiologic unit, and also present in detail the static and progressive values for many physical and physiologic constants. The book is profusely illustrated, principally with serial roentgenograms of specific bones and joints. One is impressed by the extensiveness of scope of the observations and with the wealth of data relating to each child.

As a book of reference, this volume should serve a useful purpose in many fields of child development. In this regard it deserves consideration apart from the series as a whole. The value of the data will be enhanced when interpretations are presented in the forthcoming volume III of the series.

News and Comment

GENERAL NEWS

Back Numbers Wanted.—The editor is receiving requests repeatedly from abroad for copies of the AMERICAN JOURNAL OF DISEASES OF CHILDREN and for medical books on pediatrics.

He has just received an urgent appeal from China, and has had appeals from Holland and Poland.

He will be glad to obtain back numbers of the JOURNAL from 1940 on which subscribers are not holding for their own use and also any books on pediatric subjects recently published.

He will try to see to it personally that these reach the proper persons and institutions.

Will you not please give this your immediate attention and send any material to Dr. C. G. Grulee, 636 Church Street, Evanston, Ill.?

Directory of Pediatric Societies *

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

International Congress of Pediatrics

President: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
Secretary-General: Dr. L. Emmett Holt Jr., 477 First Ave., New York 16.
Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto 2.
Secretary: Dr. S. G. Ross, 1390 Sherbrooke St. W., Montreal.
Place: New York. Time: Sept. 16-19, 1947.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

Save the Children International Union

President: Mrs. Gordon Morier.
Secretary: Dr. Georges Thélin, 43 Quai Wilson, Geneva, Switzerland.
Place: Geneva, Switzerland. Time. Sept. 17-20, 1946.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

Associação Paulista de Medicina, Secção de Pediatrias

President: Dr. Vicente Lara.
First Secretary: Dr. Armando de Arruda Sampaio.
Second Secretary: Dr. Luiz Augusto Monteiro Toledo, Av. Brigadeiro Luiz Antonio 393, 1° Andar, São Paulo, Brazil.
Time: Twelfth of every month, 8:30 p. m.

British Paediatric Association

President: Prof. G. B. Fleming, 13 Lynedoch Crescent, Glasgow.
Joint Secretary: Prof. Alan Moncrieff and Dr. Donald Paterson, Hospital for Sick Children, Great Ormond St., London, W. 1.
Place: Rugby School, Rugby. Time: Aug. 1-3, 1946.

Danish Pediatric Society

President: Dr. E. Lenstrup, Copenhagen.
Secretary: Dr. Gjørup, Dronning Louises Børnehospital, Copenhagen.

Nederlandische Vereeniging voor Kindergeneeskunde

President: Dr. J. H. G. Carstens, Servaas Bolwerk 14, Utrecht.
Secretary: Dr. R. P. van de Kasteele, Lyccumplein 10, den Haag.
Place: Children's Hospital or Pediatric Clinic. Time: Three times a year.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

PALESTINE JEWISH MEDICAL ASSOCIATION, SECTION OF PHYSICIANS OF CHILDREN'S DISEASES

President: Prof. L. F. Meyer, 29 Toelsohn St., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

ROYAL SOCIETY OF MEDICINE, SECTION FOR THE STUDY OF DISEASE IN CHILDREN

President: Prof. Norman Capon, 49A Rodney St., Liverpool, England.
Secretary: Dr. J. N. O'Reilly, 46 Harley St., London, W. 1, England.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:15 p. m.

SOCIEDAD CUBANA DE PEDIATRIA

President: Dr. Teodosio Valledor, Habana.
Secretary: Dr. Carlos Hernandez Miyares, Hospital Nuestra Señora de las Mercedes L y 21, Apartado, 2430, Habana.
Place: Cátedra de Clinica Infantil, Hospital Nuestra Señora de las Mercedas y Hospital Municipal de Infancia, Habana. Time: Last Wednesday of every month.

SOCIEDAD ECUADORIANA DE PEDIATRIA

President: Dr. Francisco de Icaza Bustamente.
Secretary: Dr. M. I. Gómez Lince, P. O. Box 693, Guayaquil.

SOCIEDAD MEXICANA DE PEDIATRIA

President: Dr. Fernando López Clares, 12/a. Medellín 191, Mexico.
Secretary: Dr. Jesus Gómez Pagola, Versalles 64, Mexico.

SOCIEDAD DE PEDIATRIA DE CÓRDOBA

President: Dr. Juan Francisco Herrera, Córdoba, Argentina.
Secretary: Dr. Bernardo Serebrinsky, Dean Funes 2000, Esq. Ocaña (N.), Córdoba. Argentina.
Place: Comite pro Defenso del Niño, Dean Funes 2000, Córdoba, Argentina. Time: Once a month.

SOCIEDAD DE PEDIATRIA DEL LITORAL

President: Dr. Jose E. Celoria, Hospital Centenario, Rosario, Argentina.
Secretary: Dr. Gloria Lovell, Hospital Centenario, Rosario, Argentina.

SOCIEDAD DE PEDIATRÍA DE SANTIAGO DE CUBA

President: Dr. Antonio Béguez César, Sagarra 107, Santiago de Cuba.
Secretary: Dra. Susana Texdó Vaillant, Padre Pico 57, Santiago de Cuba.
Place: Colegio Médico. Time: Last Tuesday of every month.

SOCIEDAD VENEZOLANA DE PUERICULTURA Y PEDIATRIA

President: Dr. Pedro J. Alvarez.
Secretary: Dr. Ernesto R. Figueroa, 3a Avenida 10, Bella Vista, Caracas.
Place: Hospital Municipal de Niños Jose Manuel de los Rios, Caracas.

SOCIÉTÉ DE PÉDIATRIE DE PARIS

President: Dr. Leveuf, Paris, France.
Secretary: Dr. Jean Hallé, 10 bis Rue Pré aux Clercs, Paris, France.
Place: Hôpital des Enfants Maladies, 149 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

SWEDISH MEDICAL SOCIETY, SECTION FOR PEDIATRICS AND SCHOOL HYGIENE

President: Prof. Arvid Wallgren, 53 Strandvägen, Stockholm.
Secretary: Dr. Henning Magnusson, 58 Odengatan, Stockholm.
Place: Various clinics and hospitals in Stockholm and Uppsala. Time: Second Friday of each month (except summer).

Uruguayan Society of Pediatrics

President: Dr. Jose Bonaba, Montevideo.
Secretary: Dr. Héctor Fossatti, Durazno 1882, Montevideo.
Place: Club Medico del Uruguay, Avenida Agraciado 1464 (Piso 13), Montevideo

NATIONAL

American Medical Association, Scientific Assembly, Section on Pediatrics

Chairman: Dr. John Aikman, 184 Alexander St., Rochester, N. Y.
Secretary: Dr. Gilbert J. Levy, 188 S. Bellevue Blvd., Memphis, Tenn.

American Academy of Pediatrics

President: Dr. Jay I. Durand, 515 Cobb Bldg., Seattle, Wash.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Place: Hotel William Penn, Pittsburgh. Time: Nov. 13-16, 1946.

American Hospital Association, Massachusetts Hospital Association

Chairman: Dr. Frank Wing, Boston.
Secretary: Dr. W. Franklin Wood, McLean Hospital, Waverly 79, Mass.
Place: Boston. Time: November 1946.

American Pediatric Society

President: Dr. Harold K. Faber, 2361 Clay St., San Francisco.
Secretary-Treasurer: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago 12.

Canadian Society for the Study of Diseases of Children

President: Dr. H. S. Little, 300 Dufferin Ave., London, Ontario.
Secretary-Treasurer: Dr. Elizabeth Chant Robertson, 67 College St., Toronto 2.
Place: Banff, Alberta. Time: June 14-15, 1946.

Society for Pediatric Research

President: Dr. Mitchell I. Rubin, 219 Bryant St., Buffalo 9, N. Y.
Secretary: Dr. Robert F. Ward, Bellevue Hospital, New York 16.

SECTIONAL

Intermountain Pediatric Society

President: Dr. Robert Alway, University of Utah School of Medicine, Salt Lake City 2.
Secretary-Treasurer: Dr. L. Paul Rasmussen, 1020 Boston Bldg., Salt Lake City 1.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

New England Pediatric Society

President: Dr. James Marvin Baty, 1101 Beacon St., Brookline, Mass.
Secretary-Treasurer: Dr. Charles D. May, 300 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Three meetings a year, occurring from September to May.

North Pacific Pediatric Society

President: Dr. Percy Guy, 502-2d Ave., Seattle, Wash.
Secretary: Dr. Aldis B. Johnson, 515 Cobb Bldg., Seattle, Wash.
Place: Vancouver, B. C. Time: Oct. 19, 1946.

Northwestern Pediatric Society

President: Dr. George B. Logan, 102 Second Ave. S. W., Rochester, Minn.
Secretary-Treasurer: Dr. Northrop Beach, 1009 Nicollet Ave., Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

ROCKY MOUNTAIN PEDIATRIC SOCIETY

President: Dr. G. R. Fisher, 23 E. Pikes Peak Ave., Colorado Springs, Colo.
Secretary: Dr. Joseph H. Lyday, 1850 Gilpin St., Denver 2.

SOUTHERN MEDICAL ASSOCIATION, SECTION OF PEDIATRICS

Chairman: Dr. William Weston Jr., 1428 Lady St., Columbia, S. C.
Secretary: Dr. Angus McBryde, 604 W. Chapel Hill St., Durham, N. C.

STATE

ALABAMA PEDIATRIC SOCIETY

President: Dr. Jerome C. Chapman, 2160 Highland Ave., Birmingham.
Secretary-Treasurer: Dr. Ruth Berrey, 2021–6th Ave. N., Birmingham.
Place: Birmingham. Time: September 1946.

ARIZONA PEDIATRIC SOCIETY

President: Dr. W. P. Sherrill, 342 W. McDowell Rd., Phoenix.
Secretary: Dr. W. F. Schoffman, 926 E. McDowell Rd., Phoenix.
Place: Phoenix or Tucson. Time: At time of state meeting.

ARKANSAS STATE PEDIATRIC ASSOCIATION

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

CALIFORNIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. Charles W. Leach, 2000 Van Ness Ave., San Francisco 9.
Secretary: Dr. Chester I. Mead, 1930 Truxton Ave., Bakersfield.
Place: Biltmore Hotel, Los Angeles. Time: May 7-10, 1946.

FLORIDA STATE PEDIATRIC SOCIETY

President: Dr. Councill Rudolph, 103–5th St. S., St. Petersburg.
Secretary: Dr. Robert Blessing, 409 Blount Bldg., Ft. Lauderdale.
Place: Concurrent with state association convention and fall meeting.

GEORGIA PEDIATRIC SOCIETY

President: Dr. Alton Johnson, 102 E. Central Ave., Valdosta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Place: Atlanta. Time: At time of annual state meeting.

HEZEKIAH BEARDSLEY PEDIATRIC CLUB OF CONNECTICUT

President: Dr. Edward T. Wakeman, 129 Whitney Ave., New Haven.
Secretary: Dr. Herman Yannet, Southbury Training School, Southbury.
Place: New Haven. Time: September 1946.

ILLINOIS STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. Craig D. Butler, 715 Lake St., Oak Park.
Secretary: Dr. A. J. Fletcher, 139 N. Vermilion, Danville.

INDIANA STATE PEDIATRIC SOCIETY

President: Dr. K. T. Knode, 1105 E. Jefferson Bldg., South Bend.
Secretary-Treasurer: Dr. Matthew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

IOWA PEDIATRIC SOCIETY

President: Dr. Arnold M. Smythe, 406–6th Ave., Des Moines.
Secretary-Treasurer: Dr. James Dunn, 414 Blackhawk Hotel, Davenport.
Place: Des Moines. Time: April 18, 1946.

Louisiana State Pediatric Society

President: Dr. S. George Wolfe, 1560 Line Ave., Shreveport.
Secretary-Treasurer: Dr. W. C. Rivenbark, 1448 Louisiana Ave., New Orleans 15.

Medical Society of State of New York, Section on Pediatrics

Chairman: Dr. Carl H. Laws, 12 Pierrepont St., Brooklyn, N. Y.
Secretary: Dr. George R. Murphy, 292 Madison Ave., New York.
Place: Hotel Pennsylvania, New York. Time: May 2-3, 1946.

Medical Society of the State of Pennsylvania, Pediatric Section

Chairman: Dr. Elwood W. Stitzel, 403 Central Trust Bldg., Altoona, Pa.
Secretary: Dr. P. F. Lucchesi, Philadelphia Hospital, Philadelphia.

Michigan State Medical Society, Pediatric Section

Chairman: Dr. Donald J. Barnes, 3001 W. Grand Blvd., Detroit, Mich.
Secretary: Dr. Mark F. Osterlin, Central Michigan Children's Clinic, Traverse City.
Place: Detroit. Time: Sept. 25-27, 1945.

Mississippi State Pediatric Society

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

Nebraska Pediatric Society

President: Dr. John M. Thomas, 1418 Medical Arts Bldg., Omaha 2.
Secretary-Treasurer: Dr. Gerald C. O'Neil, 640 City National Bank Bldg., Omaha.
Place: As announced by committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

New Mexico State Pediatric Society

President: Dr. M. K. Wylder, 221 W. Central Ave., Albuquerque.
Secretary-Treasurer: Dr. Ly Werner, 221 W. Central Ave., Albuquerque.

North Carolina Pediatric Society

President: Dr. Charles R. Bugg, Professional Bldg., Raleigh.
Secretary: Dr. Charles F. Williams, 817 Hillsboro St., Raleigh.
Place: Roaring Gap. Time: September 1946.

Northern California Pediatric Society

President: Dr. Edith M. Meyers, 431–30th St., Oakland.
Secretary: Dr. A. L. Gleason, 411–29th St., Oakland 9.
Place: San Francisco. Time: Second Thursday of February, April, September and November.

Oklahoma State Pediatric Society

President: Dr. G. R. Russell, 604 S. Cincinnati Ave., Tulsa.
Secretary: Dr. Luverne Hays, 108 W. 6th St., Tulsa.
Place: With Oklahoma State Medical Association. Time: Annual Meeting.

South Carolina Pediatric Society

President: Dr. George D. Johnson, Spartanburg.
Secretary-Treasurer: Dr. B. O. Ravenel, Roper Hospital, Charleston.

Tennessee Pediatric Society

President: Dr. F. T. Mitchell, 376 S. Bellview, Memphis.
Secretary-Treasurer: Dr. W. O. Vaughan, 2103 Hayes St., Nashville 5.
Time: Second Monday in April.

Texas Pediatric Society

President: Dr. Max Woodward, 202 N. Travis St., Sherman.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmount Ave., Dallas 4.
Place: Fort Worth. Time: Oct. 4-5, 1946.

Virginia Pediatric Society

President: Dr. Emily Gardner, 1100 W. Franklin St., Richmond 20.
Secretary: Dr. Louise Galvin, 214 S. Boulevard, Richmond 21.

West Virginia State Medical Society, Section on Pediatrics

President: Dr. Jack Basman, 1021 Quarrier St., Charleston.
Secretary: Dr. Harry E. Baldock, Medical Arts Bldg., Charleston.
Place: Huntington. Time: May 13-15, 1946.

LOCAL

Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. J. I. Hartman, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. Alexander N. Freed, 2012 W. 25th St., Cleveland.
Place: Cleveland Medical Library Bldg. Time: 8:15 p. m., October, December, February and April.

Academy of Medicine, Toronto, Section of Pediatrics

President: Dr. J. H. Ebbs, 13 Queen's Park, Toronto, Canada.
Secretary: Dr. J. F. McCreary, 170 St. George St., Toronto, Canada.
Place: Academy of Medicine. Time: 8:30 p. m., third Thursday of each month.

Bronx Pediatric Society

President: Dr. Walter Levy, 12 E. 88th St., New York.
Secretary: Dr. Joseph Blasenstein, 960 Grand Concourse, New York.
Place: Concourse Plaza Hotel, 161st St. and Grand Concourse. Time: Second Wednesday of each month, except June, July, August and September.

Brooklyn Academy of Pediatrics

President: Dr. Lambert Krahulik, 14 Sidney Pl., Brooklyn.
Secretary: Dr. Joseph Battaglia, 713 Bushwick Ave., Brooklyn 21.
Place: Granada Hotel. Time: 8:45 p. m., fourth Wednesday of February, March, April, May and November.

Buffalo Pediatric Society

President: Dr. Douglas P. Arnold, 159 Bidwell Parkway, Buffalo, N. Y.
Secretary: Dr. Richard A. Downey, 786 Forest Ave., Buffalo 9, N. Y.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p. m., first Monday of each month from September to June.

Central New York Pediatric Club

President: Dr. Arthur W. Benson, 2 St. Paul St., Troy.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Places: Various cities in New York. Time: Third Tuesday of April and October.

Chicago Pediatric Society

President: Dr. Joseph Greengard, 4753 Broadway, Chicago 40.
Secretary: Dr. Alvah L. Newcomb, 723 Elm St., Winnetka, Ill.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May inclusive.

Cincinnati Pediatric Society

President: Dr. Leo S. Friedman, 666 Rockdale Ave., Cincinnati 29.
Secretary: Dr. George Renner, 3144 Jefferson Ave., Cincinnati.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

Dallas Pediatric Society

President: Dr. O. René Caillet, 4325 Cole Ave., Dallas, Texas.
Secretary-Treasurer: Dorothy Wyvell, Bradford Memorial Hospital for Babies, Texas.
Place: Children's Medical Center. Time: 1 p. m., third Saturday and 8:30 p. m., the first Thursday of each month.

Detroit Pediatric Society

President: Dr. Otto Grob, 651 Fisher Bldg., Detroit 2, Mich.
Secretary: Dr. Harold B. Rothbart, 773 Fisher Bldg., Detroit 2, Mich.
Place: Variable. Time: Third Wednesday of each month.

Houston Pediatric Society

President: Dr. Raymond Cohen, 2300 Caroline St., Houston, Texas.
Secretary: Dr. Betty Moody, 526 Richmond Rd., Houston, Texas.
Place: River Oaks Country Club. Time: 7:30 p. m., fourth Monday of each month.

Kansas City (Missouri) Pediatric Society

President: Dr. Harry M. Gilkey, 1624 Professional Bldg., Kansas City.
Secretary: Dr. Leland Speer, 1022 Parkway, Kansas City.
Place: Kansas City General Hospital. Time: On call.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Albert L. Hill, 1401 S. Hope St., Los Angeles.
Secretary-Treasurer: Dr. Robert Simonds, 1925 Wilshire Blvd., Los Angeles.
Place: Los Angeles County Medical Headquarters, 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Henry Rascoff, 895 Eastern Parkway, Brooklyn.
Secretary: Dr. Harold Levy, 750 St. Marks Ave., Brooklyn.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., fourth Monday of each month.

Medical Society of the County of Queens, Inc., Section on Pediatrics

Chairman: Dr. Meyeron Coe, 217-02-91st Ave., Queens Village, N. Y.
Secretary-Treasurer: Dr. Louis Appel, 143-42 Cherry Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. John Washington, 2203 Wyoming Ave., Washington, D. C.
Secretary-Treasurer: Dr. George Maksim, 1418 Good Hope Rd. S.E., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N. W. Time: 8 p. m., third Thursday of October, January, March and May.

Memphis Pediatric Society

President: Dr. Kinsey M. Buck, 1193 Madison Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. Barton Etter, 1024 Madison Ave., Memphis, Tenn.
Place: Memphis Country Club. Time: 8 p. m., Dec. 13, 1946.

Milwaukee Pediatric Society

President: Dr. G. H. Fellman, 231 W. Wisconsin Ave., Milwaukee.
Secretary-Treasurer: Dr. R. P. Showalter, 411 E. Mason St., Milwaukee 2.
Place: Milwaukee Children's Hospital. Time: Second Wednesday in February, April, June, October and December.

New York Academy of Medicine, Section of Pediatrics

Chairman: Dr. Robert O. Du Bois, 122 E. 76th St., New York.
Secretary: Dr. Harold W. Dargeon, 1095 Park Ave., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from November to May, inclusive, 8:30 p. m.

Oklahoma City Pediatric Society

President: Dr. William M. Taylor, 625½ N. W. 10th St., Oklahoma City.
Secretary: Dr. Jeanne McKinnon-Shofstall, 1019 N. Lee St., Oklahoma City.
Place: Oklahoma Club. Time: Third Thursday of each month.

Philadelphia Pediatric Society

President: Dr. Waldo E. Nelson, Temple University School of Medicine, Philadelphia.
Secretary: Dr. Sherman Little, 1740 Bainbridge St., Philadelphia 46.
Place: College of Physicians, 19 S. 22d St. Time: 8:30 p. m., second Tuesday in October, December, February and April.

Pittsburgh Pediatric Society

President: Dr. Elwood Stitzel, 403 Central Trust Bldg., Altoona, Pa.
Secretary-Treasurer: Dr. C. J. Stoecklein, Medical Arts Bldg., Pittsburgh 13.
Place: Pittsburgh Academy of Medicine. Time: Second Friday in October, December, February and April.

Richmond Pediatric Society

President: Dr. Edwin L. Kendig Jr., 828 W. Franklin St., Richmond 20, Va.
Secretary-Treasurer: Dr. Thomas S. Chalkley, 1200 E. Broad St., Richmond, Va.
Place: Medical College Hospital. Time: 8 p. m., third Thursday of each month, except June, July and August.

Rochester Pediatric Society

President: Dr. William L. Bradford, 260 Crittenden Blvd., Rochester 7, N. Y.
Secretary-Treasurer: Dr. Donald D. Posson, 222 Chili Ave., Rochester 11, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee.
Time: Third Friday of each month from October to May.

St. Louis Pediatric Society

President: Dr. Joseph C. Jaudon, 337 N. Euclid Ave., St. Louis.
Secretary-Treasurer: Dr. Gilbert B. Forbes, 500 S. Kingshighway, St. Louis 10.
Time: Second Thursday of each month from October to May, inclusive.

SEATTLE PEDIATRIC SOCIETY

President: Dr. D. M. Dayton, 740 St. Helens Ave., Tacoma.
Secretary: Dr. W. B. Chesley, 1306 Madison St., Seattle 4.
Place: College Club. Time: Third Friday of each month from September to June at 6:30 p. m.

SOUTHWESTERN PEDIATRIC SOCIETY

President: Dr. Robert J. Dostal, 710 Wilshire Blvd., Santa Monica, Calif.
Secretary: Dr. H. M. Van Dyke, 541 E. Broadway, Long Beach, Calif.
Place: University Club of Los Angeles. Time: 6:30 p. m., first Wednesday in January, March, May, September and November.

UNIVERSITY OF MICHIGAN PEDIATRIC AND INFECTIOUS DISEASE SOCIETY

President: Dr. Park Bradshaw, Muskegon, Mich.
Secretary: Dr. Harry A. Towsley, 1313 E. Ann St., Ann Arbor, Mich.
Place: University Hospital, Ann Arbor, Mich. Time: Oct. 25-26, 1946.

WESTCHESTER COUNTY MEDICAL SOCIETY, PEDIATRICS SECTION (NEW YORK)

President: Dr. John B. Ahouse, 27 Ludlow St., Yonkers, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.
Place: Hospitals of Westchester County. Time: Third Thursday in November, January, March and May.

CORRECTION

In the letter to the Editor from Dr. M. G. Peterman in the June issue of the AMERICAN JOURNAL OF DISEASES OF CHILDREN (**71**:659, 1946) 0.1 Gm. in the last line should read 0.1 mg.